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VOLUME CLIV.

LECTURES

ON

PHARMACOLOGY

FOR

PRACTITIONERS AND STUDENTS.

BY

DR. C. BINZ,

ORD. PROFESSOR AND GEHEIMER MEDICINAL-RATH; DIRECTOR OF THE PHARMACOLOGICAL INSTITUTE IN THE UNIVERSITY OF BONN.

TRANSLATED FROM THE SECOND GERMAN EDITION

BY

ARTHUR C. LATHAM, M.A., M.B.OXON., M.A.CANTAB.,

RADCLIFFE TRAVELLING FELLOW IN THE UNIVERSITY OF OXFORD.

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AUTHOR'S PREFACE

TO THE

SECOND GERMAN EDITION.

In the following pages I have endeavoured to present, as far as possible in a practical form, a complete account of our pharmacological knowledge. The chapters do not correspond altogether with the individual lectures, but with this exception, the book is to all intents and purposes a reproduction, in both form and substance, of a course of lectures and demonstrations which extends over two semesters.

It is not intended that this should be a text-book of Special Therapeutics, though reference has been made to various diseases and their treatment. Cases were selected for this purpose which presented many of the conditions of a scientific experiment; such cases are often much more instructive than a number of experiments on animals.

I have avoided toxicological details, whether they refer to newly-discovered poisons, or to the effects of well-known poisons, or drugs, on particular organs, unless the details had some special significance for the medical side of pharmacology. I have also avoided any discussion on facts or theories which were not likely to be interesting to the majority of my students or readers.

The quotations from the writings of others are, with few exceptions, taken from the original works; by means of them

reference can readily be made to any other important treatise upon the subject.

One of my critics has remarked that these lectures show that pharmacology is more interesting than many physicians and students imagine. I hope this may still be said of the new edition, although in many places the text has been considerably abridged. New editions usually tend to be larger than former ones; but I have thought it desirable to take an opposite course and have condensed rather than amplified my material. Sufficient new matter has, however, been added to justify the claim that, in this edition, the work has been both improved and enlarged.

The general principles which have guided me in treating the subject of pharmacology will be found in the concluding chapter of the second volume.

C. BINZ.

TRANSLATOR'S PREFACE.

THIS translation of the second German edition of Professor Binz's lectures practically represents a new edition. A considerable amount of fresh matter has been added, and numerous corrections have been made by Professor Binz, who has also read and revised the whole of the proof sheets.

The aim of the Translator has been to give the views and statements of the Author rather than to make a literal translation, and he trusts that by so doing he has not obscured the meaning of the original.

LONDON; *November*, 1895.

CONTENTS OF VOL. I.

CHAP.		PAGE
I.	Introduction	1
II.	Anæsthetics: Ether, &c.	6
III.	Anæsthetics: Chloroform, &c.	20
IV.	Morphine and allied Drugs	47
V.	Some more recent Hypnotics	74
VI.	The Bromides—Conine—Curare	99
VII.	Aconitine and allied Drugs	136
VIII.	The Nitrites	150
IX.	Iodine and its Preparations	164
X.	Artificial Sleep—Atropine	195
XI.	Caffeine and Digitalis	228
XII.	Secale Cornutum	261
XIII.	Calabar Bean—Pilocarpine—Nicotine	275
XIV.	Strychnine—The Ammonium Salts	299
XV.	Alcohol	316
XVI.	The Ethereal or Essential Oils	349

PHARMACOLOGY.

I.

The scope of Pharmacology—Dioscorides the first to write a treatise on it—Meaning of Pharmakon—Pharmacy—Pharmacognosy—Different languages used—Pharmacodynamics—The Pharmacopœias—Pharmacology the most ancient portion of the healing art, and the one most frequently employed—The most recent in its scientific application.

Pharmacology is the term used in Germany to denote the scientific investigation—with reference specially to the requirements of the physician—of such substances as are contained in the official pharmacopœias of various countries and are employed in the treatment of disease. Moreover, corresponding with the original twofold meaning of the word *φάρμακον*, pharmacology includes the investigation of such inanimate chemical bodies as acting externally on man or his surroundings, may disturb his normal existence and so become poisons. Science, however, derives its best stimulus from the teacher's own activity in research, and we therefore include in pharmacology the search after fresh knowledge, the establishment of new facts, and the clearing up of old in both divisions.

Pedanius Dioscorides, who compiled a treatise on pharmacology in the early days of the Roman Empire, introduced the name Materia Medica, and this has been retained to the present time. One of his writings[1] which has come down to us bears the title ΠΕΡΙ ΥΛΗΣ ΙΑΤΡΙΚΗΣ.

[1] "Pedanii Dioscoridis Anazarbei de Materia Medica libri quinque," 'Commentirt von C. Sprengel, herausgegeben von C. G. Kühn.' Leipzig, 1829–30.

This was translated into *De Materiâ Medicâ* by his contemporaries, and the subject has been so designated for many centuries. In more recent years this term has fallen into disuse, because it does not include the whole subject, but signifies only the enumeration and description of medicinal articles employed internally; and the other term—pharmacology—has been adopted instead.

By the term *τὸ φάρμακον* both poisons and remedies are included, and in a form actually suitable for administration. Thus Plato calls the poisoned cup administered to Socrates *τὸ φάρμακον*. Homer (Od., iv, 230) uses the word in the same sense:

φάρμακα πολλὰ μὲν ἐσθλὰ μεμιγμένα πολλὰ δὲ λυγρά.

(Herbs, many that are healing in the cup, and many baneful.)

It was with a *φάρμακον* that Circe transformed the company of Ulysses into grizzly boars, and afterwards by smearing them with a *φάρμακον* restored them to human form again (Od., x, 235, 394). In several other passages of Homer the word occurs, sometimes with the one and sometimes the other meaning.

By the terms PHARMACY and PHARMACEUTICS we mean the scientific and practical methods by which drugs are prepared and combined for administration by the apothecary; and PHARMACOGNOSY, or a systematic knowledge of the properties and actions of drugs, is a part of this. In France and Italy they still give the name pharmacology to the first department, and call the latter *Thérapeutique* and *Terapeutica*. This is the case also in England;[1] what we term pharmacology is there a branch of Materia Medica, by which is virtually meant PHARMACO-DYNAMICS,—that is to say, the special scientific problem of determining the ACTIONS of poisons and remedies on each separate part of the animal organism. In Russia, as far as I know, they adopt the same arrangement as in Germany.

What it is necessary for the physician to know about drugs and their preparation is for the most part contained in the PHARMACOPŒIA published by official authority. The

[1] Lauder Brunton, 'Text-book of Pharmacology, Therapeutics and Materia Medica,' London, 1887, p. 3.

apothecary is bound in preparing his drugs, and in carrying on his business, to follow accurately the instructions contained in that work. Probably the first pharmacopœia was the 'Ricettario Fiorentino,' published in Florence in 1489; in Germany the first was that of Nuremberg, which was written by Valerius Cordus, and was published in 1546.[1] From that time up to 1866 and 1871, almost every German state had its own Pharmacopœia. This came to an end in 1872, when the first official edition of the 'Pharmacopœia Germanica' was published, and was followed by a second edition in 1882, in 1890 by a third, and in 1895 by a supplement. The pharmacopœia used to be published in Latin; now, however, most countries adopt their own language, but in those where several languages are spoken, Latin has been retained.

The study of the action of remedies—the most important part of Pharmacology—dates back to the earliest times of the healing art. Wherever amongst uncivilised nations a wound was to be healed or a disease cured, two methods were always employed: charms or magic words were recited over the ailing limb, or over the sick person, and aromatic and bitter herbs were applied externally, or administered as hot infusions. The spells and incantations used by our ancestors have either disappeared, or clothed in different forms have been retained by the lower classes. From herbs we have advanced to minerals also, to animal products and to the warm and saline springs of the earth. Observation combined with increased intellectual development led to diagnosis and the formulating of symptoms; books upon herbs, medicines and diseases, written in the half-barbaric times, began to accumulate; the art of printing was utilised for their production with not less zeal than for the spread of the Bible. The number of pharmacological works of the sixteenth century is very considerable, and Shakespeare was able to make the healer Cerimon say in *Pericles* (Act III, Scene 2):

[1] For further details see C. Binz, "Zur Geschichte der Pharmakologie in Deutschland;" an address (with additions) delivered at the opening of the new Pharmacological Institute of the Frederic William Rhenish University at Bonn, April 22nd, 1890. 'Klinisches Jahrbuch,' Berlin, 1890, ss. 1—75.

"I ever
Have studied physic, through which secret art
By turning o'er authorities I have
(Together with my practice) made familiar
To me and to my aid, the bless'd infusions
That dwell in vegetives, in metals, stones;
And I can speak of the disturbances
That Nature works, and of her cures."

In the drama, Lord Cerimon, it is true, succeeds by his remedies in bringing back to life the fair one whose body had been rescued from the sea; but his numerous followers in the secret art of healing were often so little successful, that even from academic chairs and downwards, all healing by means of remedies was at one time declared to be an illegitimate use of medical knowledge and skill. This was a reaction from the state of things that had long existed, when patients were regarded, not as subjects to be treated from an intimate acquaintance with disease, and after a proper diagnosis, but merely as the recipients of a prescription. Therapeutics—the cure of disease—is the ripe fruit of the tree of medical knowledge, and is consequently its final aim and effort. Andreas Vesalius, the great reformer, in the sixteenth century transferred the wild plant to a suitable soil. It has developed slowly there, though for a while exposed to evil influences, and almost uprooted by the wind of speculative philosophy. It was only through the development of experimental natural science, and of improved methods of working and of investigation in therapeutics, that a better prospect for the future has arisen.

Remedies constitute the chief part of the therapeutic apparatus; and however much this may have been here and there denied by some, facts have proved stronger than scepticism.[1]

[1] C. A. Wunderlich, a clinical professor in Leipzig, who was not himself a very strong believer in the value of therapeutics, whilst recognising the great usefulness of this sceptical tendency, expressed himself as far back as 1859 with regard to it in the following striking manner in his 'Geschichte der Medicin,' s. 360: "Moreover there arose in the Vienna School a confirmed scepticism with regard to all direct therapeutic efforts, which was by no means justified. Skoda unquestionably gave the impulse to this by his experiments with remedies. These experiments were carried out in the most cold-blooded manner without any expectation of benefiting the patient, and—owing to the incompleteness of the method adopted—they invariably failed. These

Scarcely an hour passes in which the busy physician does not apply to the powers which "dwell in vegetives, in metals, stones;" and he will do this more safely the more he recognises that the pharmacology of to-day is to be cultivated on the same lines as all the other natural sciences. The sceptic may maintain that it is yet too early to make any comprehensive retrospect of what has been so far accomplished in pure science and in practice, or to draw any comparison between the present and the past; he may point out that much has still to be settled and cleared up, and much yet to be added. But he who does not through indolence stick to old methods but is conversant with the increase of new and valuable remedies, as well as with the improved knowledge we now possess of old ones, will without difficulty arrive at the conclusion that pharmacology also has made progress and can show numerous successes both in theory and practice. And this is maintained at the present time by clinical teachers and practical physicians, although the subject appears to be treated with indifference at some of the medical schools in Germany.[1]

Various methods of classification are possible. I have adopted the clinical; it has its faults as have the others, but its advantage lies in this: it leads to the creation of a natural system—the ultimate aim of pharmacology being to provide for clinical needs—and further, it keeps us in permanent connection with that clinical work from which pharmacology has to draw, as a rule, its questions and answers. At the same time the temporary practical use is not the most prominent advantage. Prevention and cure are the special design of all medical knowledge; science itself has no special design. Only on this condition—as the history of all human intellectual effort teaches us—can science accomplish the task which has been assigned to it.

depressing views—which in the end come to this, that it matters little what is done for the patient—were specially attractive to many of the weaker brethren. Many individuals are so organised as to take a pleasure in, and think themselves superior when, proclaiming the helplessness of their art. But independently of this, professional scepticism is often the mask by which feeble thinkers endeavour to conceal the weakness of their mental powers."

[1] C. Binz, "Aphorismen über das Verhältniss der Pharmakologie zur gerichtlichen Medicin," 'Deutsche med. Wochenschr.,' 1882, s. 307.

II.

Anæsthetics—Properties and preparation of ethylic ether—Valerius Cordus its discoverer—Effect on animals and man—Its employment to prevent pain in surgical operations by Jackson and Morton in 1846*—Its dangers—Results of frequently repeated etherisation—Local anæsthesia—Its other therapeutic uses—Stimulating effect in small doses—Tests for its purity—Acetic ether—Nitrous ether—Chloric ether.*

We begin with the consideration of a small group of remedies of which it may be said, that their preparation by chemical means and the discovery of the way in which to administer them to man, rank amongst the greatest of our scientific triumphs.

For centuries surgeons had endeavoured to find some ways of rendering operations painless and, by removing the pain, obviating that shock to the system which so often interferes with the success of a severe operation; the means employed, however, were all found to be insufficient, if not actually disadvantageous. It was proved that a half-conscious patient bore a surgical operation, involving the sensory nerves, worse than one who was quite conscious, and that he also offered greater resistance to the manipulations of the surgeon; consequently in the fourth decade of this century, draughts of Mandragora vernalis and poppy juice were no longer administered in the operating theatre, and nerve compression, the magnetic sleep (so called), and Braid's hypnotic state fell into disuse, though all these things had been formerly recommended and tried for the prevention of pain. The patient operated on had simply to bear the cutting and burning of his body as best he could.

In 1847 the European world was startled in the most marked manner by a report from America, that by the continuous inhalation of sulphuric ether a harmless sleep could be produced, which quickly passed off, and during which any surgical operation could be accomplished without pain to the patient.

SULPHURIC ETHER—or, as it may be more properly termed, ethylic ether, since it contains no sulphur,—or simply ETHER, is prepared from ethylic alcohol (rectified spirit) by heating it with sulphuric acid and, when the temperature of the mixture reaches 140° C. (284° F.), supplying fresh alcohol through a tube in a continuous stream. The fluid which distils over separates into two layers; the upper one is the ether, which after further rectification presents the following characters:

A clear, colourless, very mobile liquid with a characteristic odour and taste, very volatile, boiling at 35° C. (95° F.), burning with a bright flame, and miscible in all proportions with rectified spirit and fatty oils; specific gravity 0·720; 36 parts of ether absorb 1 part of water, and at 20° C. 13 parts of water absorb 1 part of ether. It dissolves $\frac{1}{800}$ of its weight of sulphur, $\frac{1}{377}$ of phosphorus, and a considerable amount of bromine and iodine.

The production of ether from alcohol takes place according to the following formulæ:

(1) $C_2H_5.OH + H_2SO_4 = H_2O + C_2H_5.HSO_4$.
(2) $C_2H_5.HSO_4 + C_2H_5.OH = H_2SO_4 + (C_2H_5)_2O$.

That is to say: (1) Alcohol and sulphuric acid form water and sulphovinic acid (a viscid, acid fluid forming stable salts); (2) The sulphovinic acid and another molecule of alcohol again form sulphuric acid, the remaining molecules combining to form ether $(C_2H_5)_2O$. Owing to the re-formation of sulphuric acid in the process, a small amount of this substance is sufficient to convert a large quantity of alcohol into ether.

Valerius Cordus was the first who discovered ether. He was born at Simsthausen, in Hesse, in 1515; for some time was a teacher of Materia Medica at Wittenberg, and died at Rome, when travelling, at the age of twenty-nine. He

heated alcohol and oil of vitriol together, adding the alcohol in a continuous stream, and the product which floated on the top of the distillate he designated "Oleum vitrioli dulce." No attention was paid to his discovery, and it was only long afterwards, in 1729, that A. S. Froben, a German chemist in London, produced a distillate which he called ether; he kept the method of its production secret. After his death in 1741 this was made known, but meanwhile ether had also been produced in 1731 by Stahl in Berlin, and by others. It was named "sulphuric ether," being regarded as a modification of sulphuric acid, until in 1807 Boullay demonstrated that it could also be produced by using phosphoric acid.

Here is a rabbit which has been fastened by its feet to a cushion. Over its head, which is left free, I place a capacious glass that contains some tow thoroughly saturated with ether; atmospheric air is freely admitted. By means of a lever resting on its epigastrium, we have previously counted the frequency of the respirations. They were 120 to the minute; very quickly they fall to 50, simultaneously the ocular reflex disappears, but the other reflexes of the body are present—the animal is deeply narcotised. On removing the glass the number of the respirations quickly rises to 90, and soon after again reaches 120; in a few minutes the animal is as sensitive as before. I again place the glass over the animal's head, and keep it there for some time; the same results follow as before, but the reflexes entirely disappear; I can irritate any part of the animal's body without making it shrink. The pulse and respiration quickly increase in frequency after the first effect of the vapour has passed off, until they reach the normal condition. The ether after a certain time ceases to influence the cardiac and respiratory centres, and only affects those of consciousness, volition and reflex action.

Ether paralyses the cortex of the brain in a marked degree. If the cortex is laid bare, it is easy by stimulating it with the induction current to put certain muscles in action. Inhalation of ether in some measure puts a stop to this. The ganglionic cells are now unaffected, and the stimulus is not transmitted; but as soon as the adminis-

tration of ether is suspended, the contractions in the corresponding peripheral parts again take place.[1]

Anstie inhaled about thirty grammes of ether from an apparatus fastened to his face by strips of plaster. "The first symptoms were those of simple exhilaration and warmth extending all over the body: the pulse was somewhat increased in frequency, and the heart's action became strong and perceptible to myself. For more than thirty seconds I experienced no other feelings than these. A sense of numbness and indistinct tingling then began to affect the feet, and spread upwards with considerable rapidity. Almost simultaneously perspiration broke out on the forehead, and I began to be dizzy with a feeling as if the room were spinning round. I felt a strong inclination to laugh, and I believe I did so. It was now impossible for me to see the movements of the second-hand of the watch which I held in my hand, or even the large figures; my limbs felt like lead, and almost the last thing of which I was conscious was that my pencil fell out of my hand, and that I could neither see it on the floor nor move my foot to feel for it.

"On recovering consciousness I could not at first move any of my limbs, and the room still seemed to spin round; the face-piece was still firmly attached. It was some little time before I could distinguish the figures on my watch; when I had accomplished this, it appeared that thirty-five minutes had elapsed since the commencement of inhalation. I was comfortably cool, but my face was damp with copious perspiration. There was still a sensation of numbness and tingling in all my limbs, and on attempting to walk I could not manage my legs. In less than five minutes more I had perfectly recovered. All the ether in the apparatus had been used."[2]

Observations similar to these were made long before 1864, but their significance was either unappreciated or they were forgotten. As far back as 1795 Beddoes, of Bristol, related experiments made by Thornton, who by ether inhalations relieved the pain and oppression in the chest of

[1] Hitzig, 'Archiv. f. Anat. Physiol. und wissensch. Med.,' 1873, s. 402.

[2] Anstie, 'Stimulants and Narcotics,' London, 1864, pp. 295, 296.

persons suffering from pulmonary disease, and by the same means rendered a woman unconscious who was suffering from a painful affection of the breast. And as regards experiments on animals, I find a passage in the works of Paracelsus, who died A.D. 1541, which must refer to sulphuric ether, and in which he recommends its internal use, in preference to opium, for the relief of pain. The sentence is as follows:

"Hic tamen de illo sulphure sciendum hoc est, quòd ex omnibus de vitriolo extractum notissimum sit, quia per se fixum est. Deinde, iunctam sibi dulcedinem habet, vt etiam à gallinis edatur: à quo aliquandiu dormiunt; postea tamen citra noxam rursus euigilant. De hoc sulphure indicandum aliter non est, quàm quòd in morbis per Anodyna curandis, citra noxam omnem, omnes passiones sanet, et dolores omnes mulceat, calores omnes extinguat, sœva morborum omnium accidentia inhibeat."[1]

W. C. Long, a practitioner in Athens, U.S.A., in 1842 and 1843 narcotised some patients with ether who were to be operated upon, but he published nothing regarding its effects.

Charles Jackson, a chemist in Boston, U.S.A., about the same date tested the soporific effect of ether upon himself, and its complete anæsthetic effect upon his students. Jackson communicated the facts to W. T. G. Morton, a dentist, and suggested to him the use of ether as a narcotising agent during the extraction of teeth. The result was so successful that Morton suggested its use in surgical operations to Dr. Warren. The latter on the 17th October, 1846, in the presence of several medical men, removed a tumour from the neck of a man under the influence of ether. The patient was rendered insensible by Morton, the inhalation was then discontinued and the operation proceeded with. The result was that the patient recovered consciousness and experienced a certain amount of pain in the neck. On the next day a fatty tumour was removed from the arm of a woman, and at Morton's suggestion the inhalation of the ether was continued during the whole time of the operation. The success was complete. "The patient was insensible during the whole time, and was entirely unconscious." The

[1] 'Avreoli Ph. Theophrasti Paracelsi Op.,' vol. ii, p. 197, Geneva, 1658.

abolition of pain in surgical operations, a discovery so long sought after, was at last an accomplished fact.[1]

At first Jackson and Morton kept the nature of their remedy secret, and endeavoured to take out a patent for it. But the odour of the ether soon revealed the secret in America, and thence also in Europe. Jackson then published an account of the discovery in a letter read at the Academy of Paris,[2] on January 18th, 1847, and within a few months the fame and virtues of ether were known in every part of the civilised world.

We will now shortly consider some other important points associated with the narcotic effects of ether.

The healthy heart, if the amount of ether administered is not too large, is unaffected except that at first its action is stimulated. The vascular system is also unaffected, as is shown by Kappeler's numerous sphygmographic tracings.[3]

The temperature of the body sinks from ·3° to 1·5° C. (·54° to 2·7° F.)—or according to the same authority to a mean of ·68° C. (1·2° F.) in twenty etherizations,—and rises in a few hours to its previous point. The pupils are generally at first contracted and then dilated. On the whole they are not very much affected by ether.

Death can be produced directly by ether inhalation. It results from paralysis of the respiratory centre, generally whilst the inhalation is proceeding, sometimes after its discontinuance. Ether may cause death directly by the vomiting which it induces (according to Kappeler in 25 per cent. of the cases), the contents of the stomach passing into the insensitive air-passages.

If ether is often inhaled it may lead to a morbid craving for it, just as is the case with tobacco, alcohol, and morphia. Ewald of Berlin has described one such instructive case:[4]

The glowing description which Dieffenbach gave of the delights of ether inhalation induced a young man to try its effects upon himself. He was a student of philosophy, and

[1] Dieffenbach, 'Der Aether gegen den Schmerz,' Berlin, 1847.

[2] Comptes Rendus, 1847, vol. xxiv, p. 74.

[3] O. Kappeler, 'Anæsthetica. Deutsche Chirurgie,' Stuttgart, 1880, s. 161.

[4] Ewald, "Ein Aetherathmer," 'Berliner klin. Wochenschrift,' 1875, No. xi.

gradually became engrossed in theological mysticism. He saw in ethereal inhalation or stimulation a means designed to free him from material surroundings, and his first experiment was successful. Alone in his room he lay down on the sofa, poured ether on his pocket handkerchief, and inhaled its vapour. He immediately became unconscious. A series of vivid pictures—mostly of a religious nature—presented themselves, and matter, time and space no longer affected him. He fancied that whole worlds passed before him, and that he had lived through endless ages; and yet on awaking, the burning candle showed that he had not been unconscious more than a quarter of an hour. Unfortunately, he was not satisfied with what he had experienced, for he awoke just as his dream was at its brightest. It was natural he should desire to recall this wonderful and magnificent vision, but it never appeared again to him with the same splendour as at first, though he endeavoured to produce it by increasing the strength and frequency of the doses. The experiments soon became habitual, and an irresistible craving was developed; what at first had been a longing for the sublime and spiritual ended in a thirst for a stimulant which only differed from the craving for alcohol in the substance employed. At the commencement he only inhaled the vapour in his study; very soon he had no rest except when the craving was gratified. He went staggering through the streets of Berlin holding his pocket handkerchief to his nose and mouth, an habitual customer of the druggist, redolent of ether to an extent almost insupportable to his companions, and at last reduced to such a state of bodily weakness that he was obliged openly to ask for help. Mentally he was less affected than could have been anticipated; the memory had not failed, his thoughts were clear, his style flowing and elegant. On one occasion he was allowed to carry out the inhalation in Ewald's presence, and during this experiment a certain degree of intoxication was produced, wherein he talked incoherent nonsense, danced about in the room, laughed, and appeared highly amused. Narcosis was not induced. In ninety minutes he had inhaled about 130 grammes (4½ oz.) of ether. At the end of eight days his breath exhaled very distinctly the odour of ether, indicating

an unexpectedly slow elimination or destruction of it in the system.

As regards its destination in the economy, it is clear from other observations that in part it passes off unchanged in the breath. Its odour is distinctly perceptible in the abdominal and thoracic cavities of individuals in whom, previous to death, subcutaneous injections of it have been made.

Local anæsthesia is also produced by ether. That cold would produce anæsthesia has long been known, and local applications of ice and salt have been used medicinally with this view.[1] In 1854 Guérard and Richet dropped chloroform or ether on the skin, and after allowing it to evaporate were able to make painless incisions in some major operations.[2] Dr. W. B. Richardson afterwards brought this into practical use by his spray-producer. With this the mercury in the thermometer can be brought down to -15° C. (5° F.). In man, as the result of the cold produced by the spray, there is at first a burning sensation in the skin, which quickly becomes red and then in a few minutes white, hard and insensible. The insensibility is caused by the great cold resulting from the evaporation of the minutely divided ether spray, by the contraction of the vessels, and by the action of the ether on the terminal organs of the sensitive nerves. That this last-named effect is produced is shown by the fact that anæsthesia is produced when the skin is filled with blood, and when the evaporation of the ether is prevented. The anæsthesia is, however, greatest when all three conditions are acting together, especially when the part to be operated upon has previously been deprived of blood by means of an elastic bandage.

Ether which is quite free from alcohol acts better than a mixture of the two. For this reason it may be well to test the ether in the manner referred to later on.

That ether can also be applied as a local sedative internally we know from its use as Spiritus Ætheris—a mixture of one part of ether with three (two in the Ph. Brit.) of rectified spirit, formerly known under the name of "Hoffmann's

[1] J. Arnott, 'On the treatment of Headaches by benumbing cold,' Brighton, 1849; 'The treatment of Cancer by the regulated application of an anæsthetic temperature,' London, 1851.

[2] Guérard et Richet, 'Gazette des Hôpitaux,' 1854, pp. 94, 118, et 214.

anodyne." The celebrated clinical physician Fr. Hoffmann, of Halle, introduced the remedy into medical practice, having been told of it by an apothecary named Martmeyer, of that place, who had discovered its mode of production almost simultaneously with Froben. Since that time "Hoffmann's drops" have remained in use. Careful investigations as to the mode of action of this remedy have revealed nothing; nevertheless from practical experience it is well established that this remedy can be used to relieve pains in the stomach and other abdominal and pelvic organs. We may regard it as having probably a direct action on the affected nerves. Ether boils at a temperature of 35° C. (95° F.), and so must rapidly vaporize in the stomach; the vapour penetrates in all directions, easily reaching the nerve-endings in the vicinity and benumbing them. In "Hoffmann's drops" the alcohol merely dilutes the ether, and in this way it can be readily dispensed; undiluted ether is not easily poured out in drops, and it evaporates quickly in the medicine glass.

If too large a quantity of ether is swallowed at once, so much vapour is suddenly developed as to distend the stomach and to disturb the circulation in the abdomen by pressure on the blood-vessels. Further, if by the abdominal distension the diaphragm is pressed upwards, the respiration may be seriously impeded. According to Claude Bernard[1] the stomach may even be ruptured from sudden distension caused in this way.

Claude Bernard has also demonstrated[2] the following effects on the abdominal organs. If 1 to 2 c.c. are introduced into the stomach and the intestines are then exposed, we notice everywhere great enlargement of the vessels, increased secretion from the intestinal canal and more rapid absorption of its contents.

Some such action stimulating the activity of the abdominal organs may be the reason why preparations of iron containing ether are of use in cases of chlorosis, whilst similar preparations without ether have little effect.

This agrees with what I have noticed with regard to the

[1] Cl. Bernard, 'Leçons sur les effets de substances toxiques et médicaments,' 1857, p. 413.

[2] Loc. cit., p. 419.

condition of the white blood-cells in individuals after the administration of ether. After taking twenty drops the number of cells in a drop of blood taken from the finger was doubled in about ten minutes; forty minutes later the original number was again present. Five-and-twenty drops of the acetic ether, to be described presently, increased the number threefold. Alcohol does not produce this effect.[1] The only explanation, therefore, of this increase in the white corpuscles is that, in consequence of the temporarily increased activity of the abdominal organs and the dilatation of all the ducts, the lymph-glands furnish a larger number of leucocytes to the blood.

Long-continued administration of ether by the stomach is, moreover, not harmless. A case is recorded[2] of a woman who in two and a half months took 180 grammes (6½ oz.) on sugar to stimulate the appetite. The result was trembling and weakness of the limbs, spasmodic movements of single muscles on walking, noises in the ears, headache, great irritation of the stomach and general discomfort. Sleeplessness ensued on first giving up the ether; later on complete recovery took place. In the north of Ireland, ether is habitually drunk as an intoxicant; it is prepared there at a cheap rate from the untaxed methylated alcohol.[3] Results analogous to those above described are produced, but the effects, of course, are more profound according to the length of time during which the habit has been maintained.

Small doses of ether[4] taken by the mouth or injected under the skin stimulate and excite the brain, the respiration, and the heart; on this account it is much employed in threatened failure of the vital powers. In patients in this condition there is no question of pain, because most of them are in a state of unconsciousness when the ether is administered. Moreover, we can easily satisfy ourselves on animals that the pain of these subcutaneous injections is not great or lasting, as is the case when alcohol is used. Special care must

[1] C. Binz, "Ueber einige Wirkungen ätherischer Oele," 'Arch. f. exper. Path. u. Pharmak,' Bd. 5, s. 127, und Bd. 8, s. 64.

[2] G. Martin, 'Gazette des Hôp.,' 1870, p. 213.

[3] E. Hart, 'Brit. Med. Journal,' 1890, p. 885.

[4] Anstie, loc. cit., p. 331.

be taken, in injecting ether, to avoid spots where important nerves lie; as, for example, in the arm, where direct irritation of the nerve by the ether has in several cases produced incurable paralysis.[1]

In practice it is most important to bear in mind how highly inflammable both ether and its vapour are. Ether may be ignited by a flame burning at some distance from it, and, if the vapour is mixed with air, it will explode. Taking a light into a room where large quantities of ether are kept, or where it is vaporised, is extremely dangerous. The two following cases may serve as warnings. They are not the only ones that have occurred.

In Lyons, a young lady was about to have a small new growth removed from the head by the actual cautery. The surgeon put her under the influence of ether, and then the red-hot instrument was applied to the head; in a moment the whole face was enveloped in flame, the ether in the inhaler, which was still in use, being ignited, and although the flames were quickly extinguished, permanent scars on the face were the result of the want of proper care and knowledge.[2]

A physician in Germany having successfully completed a Cæsarean section and having sewn up the wound and painted the abdomen with collodion—a solution of pyroxylin or gun-cotton in ether—held a light near in order carefully to inspect the bandage. Immediately the whole body of the patient was enveloped in flames, and she died in consequence of the extensive burn.

When ether is exposed in an open vessel its vapour gravitates rapidly downwards, as it is heavier than atmospheric air in the proportion of 1 to 2·56. It may under certain circumstances be important to bear this in mind.

Ether is sometimes rendered impure by the presence of the so-called heavy oil of wine (a mixture of $C_4H_{10}SO_4$ and the radicles C_nH_{2n}) and by derivatives of fusel oil; also by free acids which are developed by exposing ether to air and light; by vinyl alcohol ($C_2H_3.OH$) and peroxide of hydrogen,

[1] Poelchen, 'Deutsche med. Wochenschr.,' 1886, s. 570; D. Wallace, 'Edin. Med. Journal,' September, 1890.

[2] 'Medic. Centralzeitung,' Berlin, 1873, s. 70.

both of which are developed in ether by keeping it. If ether is poured upon filtering paper and then allowed to evaporate, no odour should remain (absence of derivatives of fusel oil). If 5 c.c. of ether are vaporised, the resulting moist vapour must not redden blue litmus-paper (absence of sulphuric, sulphurous and acetic acids). If ether is poured over caustic potash no yellow tint must be apparent within half an hour (absence of aldehyde and vinyl alcohol). If ether is repeatedly shaken with a solution of potassium iodide and exposed to sunlight for an hour, no yellow tint should be noticeable (peroxide of hydrogen). Ether is best preserved in the dark in a cool place in brown-coloured [1] bottles filled to the top, for light and air decompose it.

Fuchsin is slightly soluble in water, readily in alcohol, but not in ether. Consequently if a crystal is dropped into ether, a red colour will immediately show itself if more than a trace of water or alcohol is present.

ÆTHER ACETICUS—acetic ether—a derivative of ether, is officinal. It is a clear, colourless, volatile liquid, of a peculiar agreeable odour, soluble in all proportions in rectified spirit and ether. One part by weight dissolves in about ten parts of water. Boiling-point 74° to 76° C.; specific gravity 0·900 to 0·904. On exposure to the air free acetic acid is formed. If the amount of this is too large, litmus paper is at once reddened, which ought not to be the case. The presence of derivatives of the higher alcohols is shown by pouring gently on sulphuric acid in a test-tube, an equal quantity of acetic ether, when a dark zone will be seen between the two liquids.

It may be prepared by heating together acetate of sodium, rectified spirit and sulphuric acid. The liberated acetic acid combines with one part of the alcohol, and distils over with the water which is formed at the same time, whilst the

[1] Blue bottles do not prevent the decomposition of ether and other similar substances when they are exposed to the action of light, a point which I have investigated in a series of special experiments ('Deutsche med. Wochenschr.,' 1893, s. 1001). The reason is evident. The *blue* rays of the spectrum are those which act chemically, and these pass through blue but not through brown or red glass.

sulphate of soda, which is also formed, remains in the retort. The following represents the change :

$$NaC_2H_3O_2 + C_2H_5.OH + H_2SO_4 = NaHSO_4 + H_2O + C_2H_5.C_2H_3O_2.$$

If I make the experiment here in the retort, you perceive at once the fruit-like aroma of the resulting acetic ether.

Acetic ether is employed as a stimulant to the nervous system generally, and locally as a stimulant to the stomach. It is preferable to ether on account of its pleasant odour and taste.

From recent experiments in my laboratory[1] I find it acts very decidedly as a general stimulant. Here is a table which exemplifies this :

Time.	Experiment.	Average amount of air inspired in 1 minute.
11.50	Rabbit weighing 1700 grammes	640 c.cm.
11.57	Injected 0·03 gramme morphia into a jugular vein	290 c.cm.
12	Injected 0·1 gr. of acetic ether in the jugular vein	435 c.cm.
12.30	0·1 of acetic ether again injected	755 c.cm.

On each occasion a corresponding result was obtained. The pain produced by the hypodermic injection of acetic ether is less than that caused by ether. The dose for adults is the same as that of ether, namely a cubic centimetre.

The following experiment shows that in large doses it induces paralysis.

I place here, under a bell-glass, a lively Esculenta, and along with it a piece of sponge saturated with acetic ether. Within five minutes the animal is completely narcotised, motionless and has ceased to breathe. The heart still beats, though with reduced frequency ; you can count the beats on the side of the chest. I expose the animal now to the air, the heart soon recovers its power and frequency, and in an hour the nervous system in no longer affected.

Nitrous Ether is officinal combined with alcohol as Spiritus Ætheris Nitrosi or *sweet spirit of nitre*. Ten parts of rectified spirit are mixed with three parts of nitric acid, and

[1] P. Krautwig, " Der Essigäther als Erregungsmittel," ' Centralb. f. klin. Med.,' 1893, s. 353.

heated until eight parts have distilled over. The product is neutralised with calcined magnesia, and re-distilled with the aid of a water-bath. It is a transparent, nearly colourless liquid, with a very slight tinge of yellow, having an agreeable, ethereal, apple-like odour and sweetish burning taste. It is completely volatile and forms a clear solution with water. Specific gravity 0·840 to 0·845.

The chemical changes which take place in the process are the reduction of the nitric acid by the alcohol and the formation of water, aldehyde and nitrite of ethyl :

$$2C_2H_5.OH + HNO_3 = 2H_2O + CH_3.COH + C_2H_5.NO_2.$$

Since pure nitrite of ethyl vaporises at a temperature of 16·4° C. (61·5° F.), and is therefore very volatile, it is in the officinal preparation combined with a large proportion of alcohol. On keeping, the aldehyde is oxidised into acetic acid, giving the liquid an acid reaction.

The vapour of undiluted nitrite of ethyl is poisonous. Flourens[1] has already shown that in animals it produces muscular spasms, universal paralysis, a brown discolouration of the blood and death. These various effects are produced by all nitrites ; but they are not developed by the administration of Spiritus Ætheris Nitrosi in the usual doses. I injected under the skin of a kitten within thirty minutes 5 c.c. The animal was deeply narcotised, but in a few hours recovered completely. In practice the Spiritus Ætheris Nitrosi is regarded as a diuretic.

Spiritus Ætheris Chlorati, resulting from the action of chlorine on alcohol, is no longer officinal. It consists of a variable mixture of chloral, ethyl chloride, aldehyde and alcohol, and in its curative action is similar to that of acetic ether or nitrous ether.

The dose of each of the above three fluids is from ten to thirty drops, generally taken on sugar with water.

[1] Flourens, 'Comptes rendus,' 1847, vol. xxiv, p. 257.

III.

Chloroform—Discovery of its anæsthetic power—Its chemical properties and preparation—Difference between its action and that of ether—Is the narcosis produced by direct action on the brain, or through changes in the blood?—Demonstration of its presence in the bodily fluids—Determination of its purity—Ethyl chloride—Ethyl bromide—Nitrous oxide gas.

It was found soon after the employment of ethylic ether as an anæsthetic that it possessed certain unpleasant properties which rendered the discovery of some other useful substance desirable. Its disadvantages in general were as follows:

The duration of the period of excitement is too long; for many purposes the anæsthesia is not sufficiently deep and prolonged; a rapid and complete return to consciousness is, moreover, relatively infrequent; there is excessive secretion of tears, saliva, bronchial mucus and sweat; the saliva and mucus may find their way into the air-passages and seriously impede the respiration; the irritating properties of ether itself may give rise to bronchitis and even to pneumonia; ether is very inflammable, and to many persons its odour is disagreeable and repulsive. In favour of ether it is generally admitted that its effect—especially upon the heart—is less poisonous than that of chloroform, and that its administration therefore requires less foresight and care.[1]

Professor Simpson, of Edinburgh, published in November, 1847, some observations which had been made chiefly on women during labour.[2] He had experimented with a consider-

[1] Compare O. Kappeler, "Chloroform *versus* Æther," 'Corresp. Bl. f. Schweizer Aerzte,' 1889 (Sonderabdruck); A. Cushing (Aberdeen), 'Zeitschrift für Biologie,' 1892, Bd. xxviii, s. 365.

[2] Amongst the various objections which were raised against the use

able number of liquids of an etherial nature without obtaining any good results, until at last he tried chloroform, a small quantity of which had been given to him by Thomas Graham, the distinguished chemist.[1]

Chloroform is a limpid colourless liquid of an agreeable etherial odour and sweet taste. Dissolves in about 110 parts of water, and in all proportions in alcohol, ether and fatty oils. Boiling point 60° to 61° C. (140°—141·8° F.). Specific gravity 1·502 (1·497—Ph. B.). It was discovered in 1831 by Liebig at Giessen, as a product of the decomposition of chloral by caustic potash ; and simultaneously by Soubeiran at Paris as a result of the distillation of a solution of chlorinated lime and alcohol. In 1834 Dumas determined the composition of chloroform, and gave it its name. He regarded it as trichloride of formyl (CH)—from formic acid—a view which is no longer adopted, though the term is still used.

It is called *trichlor-methane* because it can be derived from marsh gas or methane CH_4. One molecule of this with three molecules of chlorine give hydrochloric acid and chloroform :

$$CH_4 + 3\ Cl_2 = 3\ HCl + CHCl_3.$$

It is produced from chloral by the action of caustic potash, with the formation also of formate of potash, according to the following equation :

$$C_2Cl_3HO + KHO = KCHO_2 + CHCl_3.$$

I have in this test-tube a few grammes of powdered chloral hydrate, and pour over them a solution of caustic potash. The temperature of the mixture rises. The fluid, as you see, separates into two portions, which, though colourless, may be distinguished by their different refractive

of ether or chloroform there was also in Simpson's country one based on theological grounds. This was supported chiefly by the verse in the Bible, "In sorrow thou shalt bring forth children." Simpson replied to this in a paper entitled, 'Answer to the Religious Objections advanced against the Employment of Anæsthetic Agents in Midwifery and Surgery,' Edinburgh, 1847. This was followed by another paper of the same tenor: Prothero Smith, 'Scriptural Authority for the Mitigation of the Pains of Labour by Chloroform and other Anæsthetic Agents,' London, 1848.

[1] J. Marshall, 'Lancet,' 1890, vol. ii, p. 243.

powers. The lower portion, of higher specific gravity and not miscible with the upper, is chloroform. I can demonstrate this by adding a crystal of iodine to the liquid; the chloroform that has been formed dissolves the iodine and shows a beautiful purple-red tinge, whilst the solution of chloral remains unchanged. If I isolate the two portions by means of a separator, I can easily recognise the lower portion as chloroform independently of the colour produced by the iodine.

Chloroform is very generally obtained by heating a mixture of 30 parts of chlorinated lime, 100 parts of water and 4 parts of absolute alcohol. Aldehyde is first formed from the alcohol and then chloral. On the separation of the chlorine, hydrate of lime is formed. The latter acts on the chloral in the same manner as I have already shown potash to do: water and chloroform distil over; the latter having a higher specific gravity and not being very soluble in water, collects at the bottom of the receiver, and can be removed by a separator. It is rendered neutral by the addition of a little soda, then agitated with calcium chloride to remove the water, and rectified by distillation at a temperature of 60° C. (140° F.)

The narcosis produced by chloroform runs essentially the same course both in man and in animals as that which I have already described as produced by ether. I mentioned above some differences between them, and especially those which render the use of ether less advantageous and which made it desirable to obtain a substitute. The disadvantages of chloroform are as follows:

It affects both the heart and the arteries. For the first few minutes during chloroform inhalation the pulse increases in force and frequency; pulsation of the smaller arteries under the skin, such as the thyroidea and temporalis, is distinctly visible. This stimulating effect is soon over, and the opposite condition shows itself. The pulse becomes slower than normal, the rhythm irregular, sometimes intermittent, the apex-beat of the heart becomes less distinct; the countenance, which at the commencement of inhalation was reddened, turns gradually paler, the lips appear bluish; instead of arterial pulsation there is pulsation of the veins

in the neck,—a condition of things which, though not as yet satisfactorily explained, is undoubtedly associated with irregular and insufficient action of the heart.

R. Demme[1] states that in children during chloroform narcosis the pulse becomes slower and softer. Its frequency may be reduced in those under twelve months old to 60, in older ones to 40 beats per minute. Kappeler,[2] from the sphygmographic tracings which he has taken, draws the following conclusions:—In man the pulse of deep chloroform narcosis is a *pulsus tardus*. The rounded summit-wave and the more oblique line of descent of the pulse tracing are explained most naturally by the supposition that after the expansion of the vessel during the systole, its contraction is no longer due to the action of its muscular coat, but simply to the elasticity of its walls,—in other words, to paralysis of the vaso-motor nerves. But the appearance of anacrotism and the diminution of the dicrotic wave can only be the result of diminished arterial pressure and slowing of the circulation, and so point to a weakened innervation of the circulatory system by the action of the chloroform.

Experiments on animals bear this out, and explain what has been observed in man. The blood-pressure falls, after it has risen—sometimes considerably—at first. As the tracing shows that the tension is independent of any change in the frequency or force of the pulse, any lowering of the tension must at first be attributable to a relaxation of the vessels. It depends upon a paralysis of the vaso-constrictor centre, as has been proved by experiments upon rabbits.[3]

If both carotids in an animal are compressed the blood-pressure is instantaneously increased, owing to the vaso-motor centre being stimulated by the cerebral anæmia. If the same experiment is performed on an animal under the influence of chloroform, there is no increase, or a very slight one, in the blood-pressure. This is explained most readily by the assumption that the vaso-motor centre in the medulla

[1] R. Demme, in 'Gerhardt's Handb. d. Kinderkrankh.,' 1882, Bd. vi, s. 40.

[2] Kappeler, loc. cit., s. 31, and 'Arch. für klin. Chirurgie,' 1888, Bd. xxxvii, s. 364.

[3] Th. Knoll, 'Wien. akad. Sitzungsber.,' 1876, Bd. lxxiv, s. 233.

oblongata has previously been paralysed by the chloroform.[1]

The heart itself is also directly affected, as is shown by various facts. In the first place there is the lessening of the force and frequency of the heart's action to which we have already referred, and which has been demonstrated in animals by various observers.[2]

We may separate the influence of by far the greater part of the arterial circulation on the blood-pressure, by two methods: (1) by compressing the aorta close under the diaphragm; (2) by section of the spinal cord on a level with the sixth cervical vertebra.

In the first case the very low blood-pressure induced by chloroform remains unaltered and low; this can only be referred, therefore, to a weakening of the heart, as the abdominal vessels and those of the lower extremities, both of which have important relations to the blood-pressure, are cut off. In the second case the blood-pressure under the influence of chloroform falls very considerably, and this also can only point to enfeeblement of the motive power of the heart, since after the section of the spinal cord the systemic vessels were already fully dilated previous to the administration of the chloroform.

The BODILY TEMPERATURE is lowered by chloroform, as by ether, about 0·53° C. (·95° F.). This was the mean of twenty-three observations made by Kappeler on individuals free from fever; if seven cases are added in which fever was present, the mean would be 0·59 C. (1·06° F.). The fall does not begin until at least ten minutes after commencing inhalation, and it is generally most marked after the narcosis has passed off. It is only after a considerable time—twenty minutes to five hours—that the temperature again reaches the normal.

The cause of this cannot be due to greater dissipation of heat, for this does not take place (Scheinesson); nor to the slowing of the circulation, for this, provided it is not too considerable, does not lower the bodily temperature;[3] and

[1] Bowditch u. Minot, 'Ref. Centralb. f. d. med. W.,' 1875, s. 128.

[2] See Scheinesson, 'Archiv f. Heilkunde,' 1869, Bd. x, s. 238.

[3] D. Finkler, "Ueber d. Einfluss d. Strömungs-geschwindigkeit u. d.

the fall only begins when there is no longer diminished activity of the heart's action. The only explanation, therefore, which remains, is that heat-production is lowered by the action of the chloroform.

Cases of death from chloroform have occurred, accompanied by such sudden cessation of the heart's action as to lead to the assumption that it depended solely upon a sudden sharp stimulation of the inhibitory apparatus in the heart. This has been experimentally shown on the dog.[1] Other investigators controvert this view, and in surgical cases attribute the cause of death mainly to paralysis of the respiratory centre.[2]

In man the effect produced ON RESPIRATION at first presents individual peculiarities. The only feature which the majority of those in a state of narcosis present in common, is that after continuous inhalation the number and force of the respirations decrease. The respiratory centre is weakened by chloroform, and may speedily be completely paralysed, so that death may take place from suffocation.

I have here a large rabbit tied down with a Czermak's bandage; in the heart there is a needle with a small plume attached to it so as to make it visible at a distance. On the region of the diaphragm rests the long arm of a lever, which has also at its extremity a little plume attached to it. The animal remains perfectly still; the movements of the heart and diaphragm are consequently easily seen and watched. I now apply to the nose of the animal a sponge dipped in chloroform; the respiration and the action of the heart instantaneously cease. In about ten seconds both again recur; and then on further inhalation of the chloroform, paralysis takes place. The first sudden stoppage is the result of irritation of the trigeminus and of the laryngeus

Menge des Blutes auf d. tierische Verbrennung," 'Arch. f. ges. Physiol.,' 1875, Bd. x, s. 368.

[1] Schmey und Kronecker, 'Therapeutische Monatshefte,' 1888, s. 141.

[2] Lauder Brunton and the Hyderabad Commission for investigating the cause of Death by Chloroform, 'Lancet,' 18th January, 1890, p. 155; ibid., 21st June, pp. 1369—1393. A different view is advanced by H. C. Wood and H. A. Bare, "The Cause of Death from Chloroform," in the 'Medical News,' 28th February, 1890. Against this see E. Laurie, 'Lancet,' 1890, vol. ii, p. 1143.

superior. If both trigemini are divided, it does not occur; and if both laryngei are divided, it appears in a milder form. The olfactory nerves have nothing to do with it; it is therefore a reflex phenomenon conducted through the above-mentioned nerves. Moreover you see that the same thing can be produced with ammonia and acetic acid. Any irritating vapour, in fact, may cause it. The bearing of this, so far as the human subject is concerned, is that in some individuals immediately after the commencement of chloroform inhalation the same symptoms show themselves as are seen in the rabbit, and give rise to serious complications.

The narcotic effect of chloroform may be also induced when taken into the stomach. Anstie took 2·7 grammes (45 minims) in 45 grammes (1½ oz.) of thin mucilage, the stomach being quite empty at the time. "Great warmth at the epigastrium, and a feeling of flushing all over the body, was brought on almost at once; five minutes after taking the dose the pulse was throbbing 100 per minute and the heart beating with uncomfortable violence; a sense of decided confusion of mind also annoyed me. Five minutes later I experienced a considerable degree of nausea, and the pulse had fallen much lower, but it is impossible for me to speak to its positive frequency, as I must have fallen very soon after this into a state of unconsciousness. I recovered my senses at length, and on looking at my watch found it was forty-six minutes from the time of commencing the experiment. That it was not common sleep into which I had fallen was obvious from the fact that my lower limbs felt heavy and numb, and on attempting to stand I tumbled down. For almost two hours after this I remained in a state of great discomfort, shivering, nauseated and with aching pains in the head and in all my limbs, which sometimes assumed the sharpness of a twinge of neuralgia. It was some time, also, before I recovered my muscular sense and an accurate co-ordinating power over the movements of the limbs."[1]

The URINE after narcosis from chloroform almost invariably contains albumen and fibrinous casts. If there is

[1] Anstie, loc. cit., p. 359.

actual disease of the kidneys, or any tendency thereto, the administration of chloroform is contra-indicated.

The PUPILS are contracted during deep narcosis just as in natural sleep. The explanation is this: the size of the pupil is not dependent only on the action of light and on the power of accommodation, but also upon the psychical and sensory impressions of the external world. If the chloroform sleep was not too deep, Westphal[1] noticed that by irritating the skin or mucous membrane, or by shouting loudly into the ear, the pupils transitorily dilated. Such impressions are carried from the brain and spinal cord to the medulla oblongata, and thence to the iris by the sympathetic nerves; the stimulation of the iris brings about the dilatation of the pupil. During sleep and during narcosis this stimulation is wanting, and so the action of the contractile element in the iris predominates. At the beginning of chloroform inhalation the pupil is dilated, and very soon becomes insensitive to light. If it dilates rapidly during full narcosis, this indicates commencing suffocation dependent on paralysis of the respiratory muscles or of the heart.

The MOTOR NERVES themselves are not affected by inhalation of chloroform. If before giving a frog chloroform one of the iliac arteries is tied, and then, after complete insensibility of the animal has been induced, both sciatic nerves are laid bare and their sensibility tested with the electric current, it will be found that the two nerves are equally sensitive, although the one has been bathed with the blood containing chloroform. Even when complete paralysis of the voluntary movements of the reflexes and of the respiratory movements has been induced, the function of the motor nerves remains. It is only when the sciatic nerve is directly exposed to the vapour that its function is affected. After a short stage of increased sensitiveness paralysis occurs, and this is transitory or permanent according to the strength and duration of the application.[2]

The same may be said with regard to the SENSORY NERVES.

[1] Westphal, 'Arch. f. pathol. Anat.,' 1869, Bd. xxvii, s. 409.

[2] Bernstein, 'Moleschott's Unters. z. Naturl. d. Menschen. u. d. Tiere,' 1870, Bd. x, s. 280.

If the spinal cord of a frog is divided between the third and fourth vertebræ—cutting off at the same time the lower part of the cord from the circulation,—there occurs during the administration of chloroform a stage in which the upper half of the body is completely insensitive; the lower being quite sensitive. The chloroform has passed with the blood both to the upper and lower extremities, but it has not affected the action of the sensitive nerves in the latter, for as the result of the operation the lower part of the spinal cord is unaffected by the chloroform and can still be stimulated through the sensitive nerves of the lower extremities—the effect of this stimulation being shown by the production of convulsive movements.

The question has been largely discussed, whether chloroform—and the same holds good with regard to ether—produces its narcotic effect by *changes in the blood* or by *direct* influence on the nervous substance. Those maintaining the former view supposed either that the red blood-corpuscles or their hæmoglobin were quickly attacked, and so lost their power to carry on the oxygenation of the tissues in the usual manner; or that the chloroform, as it prevents decomposition, lessened the normal combustion process, so that the venous blood consequently became incompletely arterialised, and defective stimulation of the nervous tissue was the result.

It is quite true that when you mix fresh blood with chloroform the blood is quickly destroyed—the blood-corpuscles disappear and the blood becomes lake-coloured, a brick red deposit is precipitated, the layer above becomes darkened and when agitated with air does not become brighter. But nothing of this kind is to be seen in the blood of animals which have been rendered profoundly insensible by inhalation of chloroform, though not killed by it.

The amount inhaled evidently is not sufficient to change the normal condition of the blood. The blood becomes simply a carrier of chloroform and carries it in all directions, and when the nerve-centres are affected with the blood so charged, then the characteristic effects first show themselves. This can be demonstrated in various ways. If you take a few domestic flies, which are destitute of red blood and so

have no red corpuscles to be acted upon, and place them under a bell-glass which contains a piece of sponge moistened with chloroform, in a few minutes the creatures are narcotised.

Again, the addition of so small an amount of chloroform as can be dissolved in water, to an infusion containing large living Infusoria almost instantaneously paralyses them. The protoplasmic substance is blackened. Even the sensitive plant *Mimosa pudica* is made to sleep by chloroform. At first chloroform and ether act as irritants to the plant, the stalks fall and the leaves close. After a while these open again, but they are now no longer sensitive to the touch. This insensibility continues for several hours.

A frog whose blood has been replaced by 0·7 per cent. of salt, and which, as is well known, can under such conditions move about for hours, is paralysed by chloroform vapour just as any other frog, only more slowly.[1]

That it is precisely the central ganglia which are first affected by the chloroform needs no further demonstration on animals, as it is so often seen in man. Disturbances of consciousness and of the co-ordination of movements, sleep, insensibility to strong stimulation of the nerves, abolition of the reflexes—all these depend upon the centres in the brain and cord; cerebrum, cerebellum, spinal cord, is the natural order in which the organs are affected in normal narcosis.

The external phenomena accompanying narcosis vary in different individuals. The one goes quietly to sleep without dreaming or other disordered stimulation of the brain; to another the narcosis brings with it the most varied phantasies, which are evidenced in speech and movement. The after-effects of chloroform are just as varied. One individual feels perfectly well; another suffers from shivering, a tendency to nausea, general lassitude, headache, all of which may last some days. This difference naturally depends very much on the duration of the narcosis, also on the amount of chloroform administered, but—when the same

[1] Lewisson, "Toxicologische Beobachtungen an Entbluteten Fröschen," 'Arch. f. Anat. u. Physiol.,' 1870, s. 356; also Bernstein, loc. cit., s. 299.

quantity is administered—it is also dependent on personal susceptibility.

As regards the cases of sudden death from inhalation of chloroform, the same diversity also presents itself here. Generally the cause is sudden paralysis of the *respiratory centre*—sometimes, indeed, the heart stops before the respiration, and again in other cases paralysis of both systems takes place simultaneously, at all events without recognisable interval, as has been already mentioned (page 25). The same may be said with regard to ether.

Sometimes bubbles of gas have been seen in the blood of persons who have died under the effects of chloroform, particularly in the large venous trunks and in the heart, even when no decomposition of the body had taken place. This has also been noticed in animals,[1] and it has been determined that the bubbles consist of nitrogen. The best explanation of this remarkable condition is perhaps the following:

The lung is not, as has been generally supposed, impervious to the passage of air under the maximum pressure which may occur during life, but air may escape into the pleural cavity as well as into the blood-vessels.[2] Such a maximum pressure does occur in death from chloroform, when violent expiratory efforts are made simultaneously with closure of the glottis (Ungar). As the air is pressed from the lungs into the blood-vessels the oxygen is rapidly absorbed by the carbonised blood, whilst the nitrogen remains free.

Chloroform remains for a certain time in the system. This has long been recognised.[3] The qualitative determination may be made by heating the blood of a chloroformed animal in a water-bath, and passing the distillate through a red-hot porcelain tube. In this the chloroform is decomposed into carbon, hydrochloric acid and chlorine, the latter giving a blue colour to a piece of paper moistened with iodide of potassium and exposed to its action, or, together with the hydrochloric acid, rendering turbid a solution of

[1] Sonnenburg, 'Tagebl. d. Naturforscher-Versamml.,' Baden-Baden, 1879, s. 291; O. Kappeler, 'Archiv f. klin. Chir.,' Bd. xxxv, s. 373.

[2] R. Ewald, 'Archiv f. d. ges. Physiol,' 1880, Bd. xix, s. 461.

[3] Ragsky, 'Journal f. prakt. Chemie,' 1849, Bd. xlvi, s. 170.

nitrate of silver. This chloroform reaction has been obtained from the expired air, and from the perspiration of chloroformed dogs—from the former in a marked degree, from the latter, naturally, only in a slight degree. In the blood it is the red corpuscles especially which retain the chloroform, the serum yielding scarcely a tenth part.[1] Zweifel found chloroform in the blood of a fœtus when the mother had taken it for fifteen or twenty minutes ; he found it also in the urine of the mother when the narcosis had been considerably prolonged.[2]

The test employed by Zweifel was the carbamine reaction of v. Hoffmann. Fresh urine drawn off with the catheter, if boiled with alcoholic potash and aniline, gives the penetrating and characteristic smell of phenyl-carbamine. The reaction takes place according to the following formula:

$$CHCl_3 + 3KHO + C_6H_5NH_2 = 3H_2O + 3KCl + C_6H_5.NC.$$

The urine, after narcosis of considerable duration, contains a substance which reduces oxide of copper in an alkaline solution. The chloroform which has passed into the urine may be the cause of this ; but there is some other substance besides which is not dissipated on warming the urine, and which is neither sugar nor any other carbohydrate.[3]

After the administration of chloroform either by the stomach or the lungs to animals, the amount of chlorides in the urine is increased in a sensible degree. In one experiment in man the same condition was observed.[4] The excretion of nitrogen in the urine is also increased in a slight degree after a single ordinary inhalation, but in a marked degree after repeated doses administrated internally.[5]

If chloroform is administered to animals in a fluid state, or if it is inhaled for a lengthened period and this is fre-

[1] Schmiedeberg, 'Archiv f. Heilkunde,' 1867, Bd. viii, s. 273.

[2] Zweifel, 'Archiv f. Gynäk.,' 1877, Bd. xii, s. 235; Fubini, 'Moleschotts Unters. z. Naturlehre,' 1882, Bd. xiii, s. 5.

[3] Hegar und Kaltenbach, 'Archiv f. pathol. Anat.,' 1869, Bd. xlix, s. 437; A. Kast, 'Berl. klin. Wochenschr.,' 1888, No. 19.

[4] A. Zeller, 'Zeitschr. f. physiol. Chemie,' 1883, Bd. viii, s. 70; and A. Kast, ibid., 1887, Bd. xi, s. 277.

[5] Salkowski, 'Centralb. f. d. med. Wiss.,' 1889, s. 954.

quently repeated, distinct fatty degeneration of the organs will be produced, particularly of the heart, the liver, spleen, and kidneys, the mucous membrane of the stomach and of several of the larger muscles.[1] This fact may be the explanation why certain cases after prolonged inhalations have ended fatally, when, possibly, the result may have been wrongfully attributed to the antiseptic dressings, or to loss of blood or other causes. This degenerative change is not produced by ether, at all events it occurs much less frequently.[2]

The habitual use of moderate doses of chloroform, whether inhaled or administered by the mouth, leads to marked disturbances both psychical and assimilative.[3]

If chloroform is inhaled near to the flame of a gas-light or of a paraffin lamp, the heat and light may decompose the chloroform, oxidising it and giving rise to a suffocating vapour. The chief change is as follows:

$$CHCl_3 + O = COCl_2 + HCl.$$

The phosgene gas ($COCl_2$) so formed is quickly decomposed in damp air, with the formation of carbonic and hydrochloric acids:

$$COCl_2 + H_2O = 2\,HCl + CO_2.$$

The extremely irritating action of phosgene gas (carbonyl chloride) when inhaled may even give rise to inflammation of the lungs.[4]

The practical details with regard to the administration of chloroform previous to operations, the possible risks which may accompany its use, the increased danger which may arise from the existence of fatty heart, &c.; the way in which these complications are to be avoided—are all points spe-

[1] Nothnagel, 'Berl. klin. Wochenschr.,' 1886, No. 4; Ungar, in der 'Doctordissertation,' von W. Junkers, Bonn, 1883, und von Ph. Stommel, Bonn, 1889; ferner in der 'Vierteljahrsschr. f. gerichtl. Med.,' 1887, Bd. xlvii, s. 98. The results of Ungar's experiments were confirmed later on by Strassmann and others.

[2] Selbach, 'Archiv f. exper. Path. u. Pharm.,' 1894, Bd. xxxiv, s. 1.

[3] P. Rehm, 'Berlin. klin. Wochenschr.,' 1885, s. 317.

[4] Zweifel, 'Berl. klin. Wochenschr.,' 1889, No. 15; Stobwasser and others, ibid., Nos. 10, 13, 34.

cially belonging to lectures on surgery. We may here, however, refer to the way in which the purity of chloroform may be determined, as every physician ought to know how to apply the simple tests for this purpose.

If chloroform is agitated with water the mixture ought not to redden blue litmus paper, nor should it become cloudy when carefully poured upon a solution (1 in 120) of nitrate of silver. If chloroform is shaken with a solution of iodide of potassium and mucilage of starch, the former must not become blue nor the latter violet.

By means of these tests, which I here apply to chloroform purposely rendered impure by the addition of a little hydrochloric acid and chlorine, the presence or absence of either of these substances may be demonstrated.

To understand the last two reactions I remind you that pure chloroform, although it contains 89·2 per cent. of chlorine, holds this in such close combination that when an aqueous solution of nitrate of silver is added to it, no trace of silver chloride is formed; still less able is chloroform to separate iodine from a solution of potassium iodide.

If in a stoppered glass vessel 3 cm. wide, which has previously been rinsed out with sulphuric acid, 20 grammes of chloroform are frequently agitated with 15 grammes of sulphuric acid, at the end of an hour there must be no discolouration of the liquid. If during this period it turns yellow or brown, it contains some substances resulting from the presence of fusel oil in the alcohol from which the chloroform was prepared. It must be borne in mind that by keeping chloroform in corked bottles, discolouration readily takes place; organic substances in the cork are dissolved, and these give rise to a brownish tinge when treated with sulphuric acid.

These compounds are generally much less volatile than chloroform; the following experiment, therefore, may be employed. Dip a broad strip of filtering paper in the chloroform, and then allow it to evaporate; if pure, no odour should be left on the paper afterwards.

The specific gravity test is used chiefly to detect any adulteration with alcohol. The presence of this is not harmful, but if the amount is considerable it lessens, of course, the

value of the preparation. A slight addition of alcohol makes the chloroform more stable, and on this account the ordinary preparation contains about 1 per cent. This is also the reason why the specific gravity of the officinal preparation is lower than that which is chemically pure—1·485 to 1·489.

A more important test is the determination of the boiling point, 60° to 61° C. (140° to 141·8° F). This may be done with a flask holding about 30 c.c., to which a condenser and receiver are attached. If on gently heating the chloroform up to 61° C., fluid begins to distil over at a lower temperature, or if a residue remains afterwards in the flask which requires a higher temperature for its distillation, such chloroform is useless for medicinal purposes.

Hüter[1] has reported the case of a healthy young man who had recently met with an accident and who died after the inhalation of a very moderate amount of chloroform which had been most carefully administered. In this case there appeared to be nothing to account for the paralysis of respiration and of the heart which caused death ; the choroform was therefore analysed, with the following results :

Very impure ; only one third distilled over at 62° ; the thermometer then rose rapidly to 70° and 75°, and even at 80° there was a considerable residue. Directly the flask was opened a strong odour of chloride of carbon and phosgen gas could be recognised. Hydrochloric acid and free chlorine were not present. The chloroform appeared to have been prepared from impure alcohol, and contained, as the boiling point already indicated, combinations of chlorine and the higher radicles.

The decomposition of chloroform already described as produced by a hot gas-flame also takes place when chloroform stands for some time in diffused daylight. It is therefore important that this remedy should be kept in a dark place, or in brown-coloured bottles.

But the purest chloroform may also give rise to death from causes which at present are quite obscure. The most important precaution, though this sometimes fails, is to induce narcosis *slowly*. I can demonstrate this to you on

[1] Hüter, 'Berlin. klin. Wochenschr.,' 1866, s. 303.

the dog. This animal is much more sensitive to chloroform than man is, and a very small excess kills it. If I proceed, however, with especial care, I can make the dog completely insensible without any material risk, and can keep it in this condition for a considerable time.

One part of chloroform is slowly soluble in about 110 parts of water; this solution, and even one of 7·5 to 1000, prevents in a high degree decomposition and fermentation on account of its poisonous action on the lowest organisms.[1] Chloroform on this account is useful in the preparation of subcutaneous injections, for preserving urinary specimens and titrations which easily undergo decomposition, and for preserving watery solutions of ferments. By passing a current of air through these or by warming them, or by applying both means, the chloroform is dissipated.

A saturated solution of chloroform in water poured off from the undissolved portion, and then diluted with an equal part of water, is recommended for the relief of pain in the stomach.[2] As the German Pharmacopœia fixes 0·5 gramme (7·5 drops) as the largest single dose, and 1 gramme (15 drops) as the largest quantity to be given in twenty-four hours, the above solution should be administered in doses of a tablespoonful. Generally, however, you should begin with a more dilute solution, and special watchfulness must be given at the commencement with regard to the local and stimulating effects of the remedy.

Up to the present time ether in the form of spray has usually been employed to produce anæsthesia of superficial parts of the skin or mucous membrane, the insensibility being in some measure induced by the resulting cold. Now, however, ETHYL CHLORIDE (C_2H_5Cl) or chlorethane is used, and produces much better results. This substance is prepared

[1] Salkowski, 'Deutsche med. Wochenschr.,' 1888, No. 16; P. Unna, 'Monatsschr. f. pr. Dermatol.,' 1888, No. 9; M. Kirchner, 'Zeitschr. f. Hyg.,' 1890, Bd. viii, s. 465; Stepp, 'Münch. med. Wochenschr.,' 1889, No. 8.

[2] Bianchi, 'Petersb. med. Wochenschr.,' 1888, No. 14.

by heating ethyl alcohol and hydrochloric acid under pressure. It is a colourless mobile liquid with an agreeable smell and a sweet burning taste, boiling at 12·5° C. (54·5° F.). In consequence of this low boiling-point, ethyl chloride, if put into a bottle to which a pointed tube is attached, can be expelled as a fine spray by the mere warmth of the hand. The part to which it is applied becomes bloodless, almost frozen, and absolutely insensible, so that superficial operations of short duration can then be performed without pain. That the cold due to evaporation is not the principal factor causing the anæsthesia, can be inferred from what we know regarding the corresponding action of chloroform.[1] If a cupping-glass is filled with chloroform and placed on some portion of the skin, then anæsthesia is brought about although there can be no evaporation. It is preceded by distinct irritation, and may, so it is said, cause sloughing of the skin.

The great cold which is produced by ethyl chloride may cause subsequent pain and destruction of the skin if it is applied for too long a time.

A large number of substances have been suggested for use instead of chloroform, but none, up to the present time, have superseded it. I may refer those who are specially interested in the subject to the monograph of O. Kappeler which has been already referred to, and to other literature[2] on the subject. One only of these proposed substitutes has been sufficiently often employed to justify its addition to the German Pharmacopœia. This is Ethyl Bromide—a clear, colourless, volatile, highly refractive liquid, with an agreeable ethereal odour. It has a neutral reaction, is insoluble in water, but is soluble in alcohol; it boils at 38° to 40° C. (100·4°—104° F.), and has a specific gravity of from 1·445 to 1·450. It is prepared by heating together potassium bromide, alcohol, and sulphuric acid. Its composition is C_2H_5Br. It was first employed by Nunnely in England in 1849.

When inhaled in the same way as chloroform it seems to

[1] Paschkis und J. Wagner, 'Neurolog. Centralb.,' 1886, No. 18.

[2] E. Tauber, 'Die Anaesthetica. Eine Monographie.' Berlin, 1881; Eichholz und Geuther, "Das Methylenchlorid (CH_2Cl_2) als Narcoticum." 'Deutsche med. Zeitung,' 1887, No. 67.

act somewhat more rapidly than the latter, but the effect is not so deep nor so lasting,[1] although it continues longer than is the case with nitrous oxide gas. Ethyl bromide rarely causes vomiting. It is less dangerous than chloroform, but the greatest caution is necessary when administering it to patients who are suffering from consumption or disease of the heart or kidneys. Fatal results in such cases are on record; in one a young man with tuberculosis and kidney disease succumbed to 15 or 16 grammes, whilst in another, 150 grammes—a very large dose—proved fatal to a woman during the performance of ovariotomy.

Further experience has revealed a certain peculiarity which occasionally shows itself with regard to the effects of ethyl bromide, and which deserves attention. It is this. Sometimes in a few hours after a patient has apparently quite recovered from the narcotic effects of the inhalation he is seized with a feeling of general and extreme weakness. Such an occurrence took place in this district.[2]

"The patient, a young lady of nineteen, with a view to having some teeth extracted, was narcotised with about 15 grammes of ethyl bromide. After a few inspirations she became much excited, and then in a minute and a half tranquil narcosis was induced, during which the stumps were removed. Ten minutes elapsed before consciousness returned. The patient then drove home. Two hours after the narcosis Bönnecken found her in a state of profound coma. The hands and feet were cold, the pulse small and scarcely perceptible, the breathing shallow and somewhat hurried; every three minutes it became more laboured and deeper, and ceased for half a minute. On being roused by means of counter-irritants applied to the skin the patient complained of want of breath, and numbness of the hands and feet. On trying to take coffee or champagne she had great difficulty in swallowing. After an injection of camphor the pulse rallied and soon became stronger. The disturbed

[1] L. Szumann, 'Therapeutische Monatshefte,' 1888, ss. 155 und 226. This also contains several references to the literature of the subject. E. Haffter, 'Festschrift zu Ehren C. Kappeler's.' Basel, 1890, s. 53.

[2] Bönnecken; a paper read at the meeting on the 28th May, 1894, at Bonn, of Die Niederrheinischen Gesellschaft f. Natur. u. Heilkunde.

respiration and the disordered sensations continued for nineteen hours after the narcosis. A large amount of acetone and of aceto-acetic acid was found in the urine which was passed during the following night."

This injurious after-effect of ethyl bromide evidently is dependent upon the products of its decomposition remaining in the organism for a considerable time, for, as I shall point out later on, the preparations of bromine are eliminated at an unusually slow rate from the system.

In employing this drug the following points are to be noted:—Complete narcosis is only obtained when the face-piece is thoroughly moistened and closely applied over the mouth and nose. From 10 to 30 grammes are sufficient to produce narcosis. Bromide of ethyl readily undergoes decomposition, and is therefore kept in brown-coloured bottles to prevent the action of light upon it; each bottle contains 30 grammes (463 grains). A specimen which has become in the slightest degree discoloured, must not under any circumstances be used. Decomposition is very readily induced if the liquid is exposed to the light from a gas-flame. This change may be detected by the offensive bromine-like odour which is developed. Ethyl bromide is so slightly inflammable that the caution indispensable when ether is employed is not necessary. If the narcosis is of long duration the breath of the patient smells for several days like rotten apples, or has a disagreeable odour like garlic.

On several occasions the poisonous ethylene bromide ($C_2H_4Br_2$) has been mistaken for ethyl bromide. This is likewise a colourless liquid with a pleasant flavour, but with some practice it can easily be distinguished, even when held in the hand, by its specific gravity (2·163), which is much higher than that of ethyl bromide. Its boiling-point is also higher, 129° C. (264° F.). The danger of such a mistake, however, has been considerably diminished since ethyl bromide has been included among the officinal remedies.

In 1776 Priestley discovered NITROUS OXIDE GAS, and called it dephlogisticated nitrous air. Humphry Davy dis-

covered its composition, and in 1799 found out its intoxicating effect by experimenting upon himself. Nitrous oxide gas has a faint odour and sweetish taste, is heavier than atmospheric air (1·527), and is more soluble in water than the latter. Its composition is N_2O. One method of preparing it is by reducing nitric oxide gas by means of zinc or iron filings:

$$2\,NO + Zn = N_2O + ZnO.$$

It is, however, generally made by heating ammonium nitrate, a crystalline salt which melts at about 170° C., and which is decomposed on heating into nitrous oxide gas and water:

$$NH_4NO_3 = 2\,H_2O + N_2O.$$

Chlorine—due to the frequent presence of ammonium chloride—and nitric acid gas, which is given off if the salt is heated too much, may be present as impurities; to remove these the gas is passed through several bottles containing caustic potash and sulphate of iron.

Sir H. Davy, though he only knew of the intoxicating effect of this gas, had the idea that it could produce complete insensibility. "As nitrous oxide in its extensive operation seems capable of destroying physical pain it may probably be used with advantage during surgical operations in which no great effusion of blood takes place." This prediction was fulfilled—though not until 1844—when H. Wells, an American dentist who, having witnessed the intoxicating effects of the gas at a lecture on chemistry, conceived the idea of using it for the purpose of lessening sensibility. He had a decayed tooth extracted by Dr. Riggs during narcosis induced by nitrous oxide, and then made great efforts to introduce it into general use. The introduction, however, of ether and chloroform a few years afterwards made this impossible, and so Wells failed in the attempt. Nevertheless, in 1863, Colton, the chemist through whom Wells had become acquainted with the gas, succeeded in making its use popular by persuading a few American dentists to try it in a series of cases. In 1868 the action of the gas was thoroughly investigated in Europe, and on March 31st of that year, at the Dental Hospital in London, the first tooth was extracted whilst the patient was under its

influence. Since that time its use has been indispensable in dental operations.

If the gas is inhaled with as much oxygen as the atmospheric air contains—namely 21 per cent. by volume—it shows its intoxicating influence. After it has been taken for about two minutes, the effects, according to L. Hermann,[1] are as follows :—Buzzing in the ears, indistinctness of vision, an increased feeling of heat over the whole body, and irritability of the limbs with a feeling of lightness which is probably due to loss of the muscular sense. Voluntary movements become ataxic ; the patient, when standing, oscillates ; when sitting, rocks violently to and fro. Sensitiveness to pain is somewhat lowered, the imagination becomes lively, and loud laughter sometimes occurs. The rapidity of the pulse is slightly increased, the face becomes somewhat red, and the pupils dilate. If now the inhalation is discontinued the individual quickly returns to his normal condition, though in some persons for a short period there may be a feeling of drowsiness.

If the gas is inhaled undiluted, without any admixture of atmospheric air, but with a free escape of the carbonic acid from the lungs into the air when the patient expires, the process is much more rapid. There is a brief feeling of intoxication associated with noises in the head ; the pulse becomes somewhat more frequent and fuller ; the carotids beat perceptibly ; respiration is regular and deep ; dream-like visions pass before the mind and quickly vanish again ; screaming and violent movements are not unusual ; the patient, if sitting, slips down, his muscles being relaxed ; he becomes unconscious, and the peripheral nerves are insensible to any stimulus—all this takes place in somewhat less than a minute. On discontinuing the inhalation of the gas and freely admitting air, the patient returns to consciousness within a minute, and soon afterwards recovers his normal condition, though a feeling of fatigue may last for some time. Such were the appearances which I noted in an experimental investigation to which Hugo Schulz—my assistant at the time—submitted himself. There was a complete absence of any symptoms of impending suffocation.

[1] L. Hermann, 'Lehrb. d. experiment Toxikologie,' 1874, s. 244.

A careful analysis of the symptoms accompanying this narcosis shows that it runs the same course as is the case under chloroform or ether. The cortical substance of the brain is the first part of the nervous system to be affected, and it is affected more strongly than the other parts. Next follow the spinal cord, the medulla oblongata, and then the heart. The cornea appears to be unaffected for some time, as when touched it responds—by the closing of the eye-lid—even after consciousness and the power to will have vanished. With the disappearance of the narcosis the organs recover their functional activity in the reverse order.

An English committee, appointed for the purpose of determining the relative time occupied by the various stages in the process, examined 1380 cases. The following are the averages at which they arrived :

From 63 to 80 seconds were required to produce anæsthesia ; the anæsthesia lasted from 22 to 28 seconds ; 100 to 120 seconds elapsed from the commencement of the inhalation to complete recovery. In children narcosis occurred sooner than in adults.

Complete anæsthesia is the result of the direct narcotic effect and of commencing suffocation. It was formerly believed that nitrous oxide alone was sufficient to maintain the process of oxidation which is necessary to life. It is quite true that the gas sustains combustion better than atmospheric air, much in the same way, though not so well, as free oxygen. I place a glowing chip in this glass bell-jar, which is filled with nitrous oxide ; it lights up immediately. This, however, does not hold good when applied to the blood. I have here some venous blood, and I pass nitrous oxide into the bottle until all the superincumbent air has been expelled, and then shake the bottle. The blood does not assume an arterial red colour. If I were to kill a warm-blooded animal here by allowing it to inhale pure nitrous oxide, it would die, as you would see, from want of breath and with convulsions, whilst its blood would have a dark venous colour. The unconsciousness and anæsthesia which occur when the pure gas is inhaled without oxygen, must depend for the greater part on its directly paralysing effect upon the ganglion cells of the brain, and not solely, as was formerly supposed, on

commencing suffocation. This can be shown by simple experiments with animals.[1]

Two sufficiently wide glass tubes, about 15 centimetres in height, one of which is filled with pure N_2O and the other with pure hydrogen, are placed in a mercurial trough. I now introduce through the mercury into the former a healthy frog, from the lungs of which I press—underneath the mercury—as much air as possible. To one of the hind feet of the animal a thread is fastened. The frog, which at first is very restless, becomes almost motionless within a few minutes. Five minutes later the leg, when pulled out, does not react to the application of acetic acid, although there is an occasional respiratory movement. The animal is now placed in the air, and after thirty seconds it responds to the stimulation of the acid, though it still lies upon its back. A few minutes later it recovers itself.

The same animal is now placed in the hydrogen jar. Violent restlessness and laboured respiration are brought about, and last longer than in the former experiment. Gradually the frog becomes quiet, without, however, losing the power of sensation or of reflex excitability; for even after ninety minutes it responds when the thread is pulled, and still more so on the application of acetic acid. In the hydrogen the reflex excitability was retained, whilst in the nitrous oxide it quickly disappeared.

That the absence of oxygen is, after all, necessary for speedy and complete anæsthesia is shown by the following experiment:—A healthy frog placed in a bell glass filled with nitrous oxide ceases to respond to mechanical and chemical irritation within fifteen minutes. If now a quantity of air—representing but a small percentage of the whole mixture—is introduced into the glass, the animal rapidly regains its irritability. On repeating these experiments with warm-blooded animals, similar results are obtained. With nitrous oxide the feeling of want of breath is much slighter than with an indifferent gas. In the latter case convulsions are observed; in the former case these are either absent or unimportant.

As is the case in ordinary suffocation, three stages can

[1] Zuntz und Goldstein, 'Arch. f. ges. Physiol.,' 1878, Bd. xvii, s. 344.

be distinguished during the process of inhaling pure nitrous oxide: (1) increased inspiratory efforts; (2) violent, active expiratory efforts; (3) isolated inspirations which gradually become shallower, but which continue until the respiratory centre is paralysed. After the supervention of these inspirations it is still always possible to restore the animal by means of artificial respiration. Anæsthesia, when due to nitrous oxide gas, always accompanies the second stage—that is, the stage of active expiratory effort. If the administration of the gas is then discontinued, anæsthesia still persists for about a minute. By carefully observing this condition, the possibility of suffocation is almost entirely obviated.

In making comparisons between the two it is further important to observe that in simple suffocation—without nitrous oxide—anæsthesia occurs only after the third stage has been reached.

These experiments on animals have therefore proved nitrous oxide to be a true and direct narcotic. Since 1863 it has been constantly employed in practice, though the extent of its application has certainly been somewhat limited. The short duration of the complete narcosis and the great danger there is to life, if we endeavour to prolong the narcosis by a further administration of the pure gas and exclusion of air, have limited its use to the short operations of dentistry. In these we justly appreciate the rapid and temporary action of the gas, the speedy restoration of the patient to his normal condition, the almost complete absence of unpleasant after-effects, and the very small risk attendant upon its administration. The number of deaths caused by nitrous oxide is extremely small,[1] not only in comparison with the number of cases in which it has been successfully administered, but also as compared with the fatal results occurring under the use of chloroform or ether.

In midwifery practice also it appears that nitrous oxide may be usefully employed. With reference to this, S. Klikowitsch[2] reports as follows:

[1] 'Lancet,' 1889, vol. ii, p. 804.

[2] S. Klikowitsch, 'Archiv für Gynäkologie,' 1881, Bd. xviii, s. 81, and 'Petersburger med. Wochenschr.,' 1880, ss. 115 und 249.

After he himself had taken five deep inspirations from a mixture of 80 per cent. nitrous oxide gas and 20 per cent. oxygen, he observed that the skin of his hand had become almost insensible even to the sharp prick of a needle. It appeared to him that this property of the drug might be of service, especially during the pains of childbirth, and in twenty-five consecutive cases of labour this surmise was found to be correct. A few deep inspirations of the above-mentioned mixture sufficed to free the parturient woman from pain, whilst consciousness remained undisturbed. The labour pains were not lessened, nor were any injurious effects experienced either by mother or child. It even seemed that vomiting was stopped by the inhalation. The truth of the last point Klikowitsch proved by experimental observation. Apomorphine was injected into dogs in doses which, though small, were certain to induce vomiting. The animals were then placed in a chamber containing a mixture of gases in the above-mentioned proportions. The vomiting was either altogether prevented, or else it came on considerably later than usual.

S. Klikowitsch also used this mixture of gases successfully in relieving the symptoms of certain diseases. It seemed to alleviate the nervous symptoms associated with insufficiency of the semilunar valves and an aortic aneurism; also those in angina pectoris, in bronchial asthma and in phthisis. Improved sleep, considerable diminution in the frequency of the cough, a lessening of the feeling of suffocation, and a diminished frequency of the pulse were observed. The following experiment has been reported:[1]

If a dog is made to inhale pure nitrous oxide for a minute, and is then given a mixture of gases in which the nitrogen of atmospheric air is replaced by nitrous oxide, *i. e.* 21 per cent. O_2 and 79 per cent. N_2O, the animal can be kept for over half an hour in a condition of complete anæsthesia without any injurious result. This accords almost completely with Klikowitsch's experiments upon

[1] P. Bert, 'Gazette méd. Paris,' 1878, pp. 79, 108, 123, 274, 498, 579; 'Compt. Rend.,' 1883, tom. xcvi, 30 Avril. See also Tittel (Dresden), 'Centralbl. für Gynäkologie,' 1883, s. 165; A. Döderlein, ref. 'Centralbl. f. d. med. Wiss.,' 1886, s. 439.

himself and on parturient women with the same mixture of gases. The supply of sufficient oxygen to support life prevents suffocation, and the large amount of nitrous oxide contained in the mixture maintains the deep narcosis which this gas alone had primarily induced. The cells of the brain do not recover with the same rapidity as before, for the nitrous oxide is now sufficient to keep down the vitality which has been already lowered, even though oxygen is administered at the same time.

The supposition[1] that all the inhaled nitrous oxide leaves the organism unchanged is arbitrary so far as our present knowledge goes. Hitherto, for very good reasons,[2] such an analysis has not been effected. The possibility that this gas is decomposed in the nervous centres—as by an incandescent body—into nitrogen and oxygen, if only in very small quantities, has still to be demonstrated.

When nitrous oxide is administered with the view of inducing narcosis, it is respired from a gasholder, or iron flask, through a tube terminating in an india-rubber mouthpiece. This either encloses the mouth and nose like an air-tight mask, or it is placed between the teeth, the nasal orifice being simultaneously closed. In either case when the patient inspires he receives the gas alone. A valve allows the air from the lungs to pass out into the atmosphere, and another opening, which can easily be adjusted, allows the admixture of air during the inhalation.

In order to lessen the inconvenience in administering the gas, and to facilitate its transport, it is stored in iron bottles, having been reduced to a liquid form under a pressure of thirty-two atmospheres. The bottle is placed in a case, and, by means of a tap and tube attached to it, is connected with an empty india-rubber bag. If the tap is turned, the liquid under reduced pressure becomes gaseous and streams into the bag. When this is filled the tap is turned and the supply cut off. By pressure upon the bag the gas now passes with each inspiration of the patient into his respiratory passages.

Ozone and nitrous oxide both possess this in common

[1] H. Wood and Cerna, 'Therap. Gazette,' 1890, August.

[2] Goldstein und Zuntz, loc. cit., 335.

that they each have an atom of oxygen available for oxidising purposes. Ozonised air also, when inhaled in very large quantities, provided it does not give rise to coughing, can produce a sleep similar to the narcosis of nitrous oxide. This I have proved by a number of experiments,[1] chiefly on the human subject, and the results have been confirmed by others.[2] With our present knowledge there is only one possible explanation of the process; the ozone permeating through the very thin tissue of the pulmonary alveoli into the blood, forms in it a compound which, on being carried to the brain, acts, under favourable conditions, as a mild and transient soporific.

This property of ozonized air has not as yet become of practical utility or importance.

[1] C. Binz, 'Berl. klin. Wochenschr.,' 1882, Nos. 1 and 2.

[2] Filipow and Dogiel, compare 'Berl. klin. Wochensch.,' 1884, No. 40. See also the experiments of E. de Renzi, 'Archiv für. Pathol. Anat.,' 1886, Bd. civ, s. 203; and my condensed account in 'Eulenburg's Encyklopädie d. ges. Heilkunde,' 1888, Bd. xv, Artikel "Ozon."

IV.

Opium—Its origin—Constituents—Chief alkaloids—Morphine—Narcotic effect—Poisonous action—Effect on the spinal cord, heart, &c.—Its powers of lessening the peristaltic movement of the intestine—Narcotine, Thebaine, and Codeine—Subcutaneous injection of morphine—Its advantages and disadvantages—Excretion of Morphine—How to recognise it and to determine its purity—Meconic acid, a means of determining the presence of opium and its extracts—Opium smoking—Substitutes for opium—Cannabis Indica—Haschisch—Lactucarium.

The wall of the seed capsules of *Papaver somniferum* contains—immediately after the flowers have fallen—a white, milky juice, which flows out when superficial incisions are made in the capsule. It is then scraped off, and after being dried in the sun has a red tinge, which on exposure becomes darker and changes into a reddish brown colour. Whilst still moist it is collected into fairly large masses; these are wrapped in poppy leaves and sold as opium cakes. The poppy plant is cultivated for the production of opium in several countries; even in Germany this has been done successfully. For medicinal purposes, however, the opium grown in Asia Minor is employed, for only this kind contains a sufficiently constant percentage of active material to allow of an accurate adjustment of the dose. The poppy plant was known in Germany as early as the Middle Ages, but the mode of obtaining opium was acquired later. This knowledge seems to have been brought to us after the Crusades, and since then to have slowly spread through the country.

The drug consists, for the most part, of ordinary vegetable products, such as albumen, sugar, mucus, fatty matter, salts,

etc. It should contain 10 per cent. of morphine, the principal and most active of the eighteen alkaloids which have been found in it. In former times crystals had already been obtained from it and called Magisterium Opii. It was in 1816 that the apothecary, Friedr. W. A. Sertürner, in Einbeck (Hanover), succeeded in obtaining morphine in a pure state. He determined its chemical nature, and showed that the effect of opium on man was essentially due to this ingredient.[1]

All other discoveries and statements concerning the alkaloids—quinine, atropine, strychnine, &c.—are for the greater part only repetitions of what the obscure Hanoverian apothecary had done seventy-five years ago under the greatest difficulties. This was the starting-point for the discovery of all alkaloids which now play so important a rôle in pharmacology, because it is only by using these alkaloids that we can give an accurate dose to a patient and scientifically study its effects.

These bodies are called alkaloids, because they have similar properties to those of the alkalies.

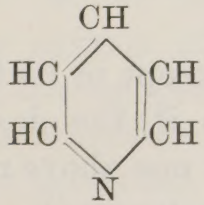
They turn the colour of red litmus to blue. I add here, to some tincture of litmus in a test-glass which has been made red by the addition of a little hydrochloric acid, a solution of cinchonine hydrate in alcohol; the colour at once turns blue. With acids alkaloids form characteristic salts; thus if I were to allow this liquid to evaporate, a crystallised salt—cinchonine hydrochlorate—would remain behind. If electrolysed these bodies are electro-positive, as is the case with the metallic bases; for this reason formerly, when the name was in an abbreviated form, the corresponding sign was added; the first letters were given and the sign placed above, thus morphine = M $\dot{\text{o}}$. Alkaloids resemble alkalies also in their stability. Being organic bodies they readily burn when heated, giving off and leaving a considerable residue of carbon. In the

[1] Sertürner, "Ueber das Morphium eine neue salzfähige Grundlage, und die Mekonsäure, als Hauptbestandteile des Opiums," Gilbert's 'Annalen der Physik,' 1817, Bd. 55, s. 56. Sertürner, "Ueber eins der fürchterlichsten Gifte der Pflanzenwelt," a supplement to my paper "Ueber die Mekonsäure und das Morphium," ibid., 1817, Bd. 57, s. 183.

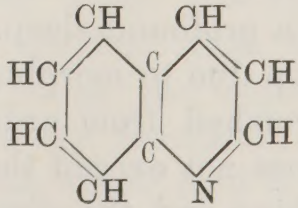
animal organism they remain to a considerable extent unchanged, so that they can be detected afterwards in the urine. Alkalies generally precipitate them from their salts: thus if I add caustic soda to a solution of cinchonine hydrochlorate, the cinchonine is precipitated in flocculent masses. The alkaloids are precipitated by a number of reagents, those most employed being phospho-molybdic acid, potassio-mercuric iodide, and iodine in a solution of potassium iodide. The latter reagent causes a thick, brown deposit which is insoluble when added to a drop of sulphuric acid. Each alkaloid has its own special reactions by which it can be identified; with some of these we shall have to deal, and further reference will be made to them.

All alkaloids consist of carbon, hydrogen and nitrogen. Most of them contain oxygen also, but this is not an essential characteristic.

As regards their constitution, some of them may be looked upon as derivatives from ammonia. For instance, in Chenopodium vulvaria, s. olidum, *stinking goosefoot,* as well as in herring pickle, we find propylamine and trimethylamine, the latter being ammonia in which the three atoms of hydrogen are replaced by three molecules of methyl, thus $N(CH_3)_3$. Those, however, with which we are concerned, are derived from the benzene nucleus. If in this we replace a CH by N we obtain pyridine C_5H_5N, and if we double the benzene nucleus and replace a CH by N we obtain chinoline C_9H_7N, both of which are strong basic compounds which we can obtain from the officinal alkaloids by heating them with caustic potash; these bodies, according to modern chemical opinions, are the nuclei of the alkaloids. Around them other combinations are grouped, the nature and position of those with a high molecular formula being still undetermined.



Pyridine.



Chinoline.

The alkaloids, so far as the vital processes in plants are concerned, must be regarded chiefly as excretory products. They are the result of tissue change in the plants, are deposited in them as salts, and are not turned to any further use.

Of all the alkaloids contained in opium, MORPHINE is by far the most important. The hydrochlorate in the form of fine rhombic prisms is officinal. Its formula is $C_{17}H_{19}NO_2$, $HCl + 3H_2O$.

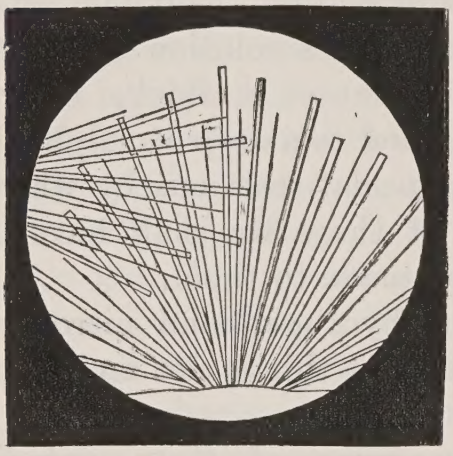


FIG. 1.—Hydrochlorate of morphine, crystallised from aqueous solution. Slightly magnified.

The following are the symptoms which usually present themselves in the human subject after a subcutaneous injection of one centigramme (about one sixth of a grain) of morphia in one cubic centimetre of water :

After a few minutes there is an undefined feeling of general comfort. The mental faculties are agreeably stimulated, the brain seems more active and without any sense of oppression. Fantastic lights and glimmerings appear before the eyes. There is a desire to remain undisturbed, the slightest attempt at movement is a trouble. Questions are only answered indefinitely ; glimpses of indistinct, agreeable visions appear. All these pleasant feelings, however, are of short duration. The eyelids begin to droop, the individual who, in the previous enjoyment of comfortable repose, was disinclined to move his limbs is now unable to do so. Every impulse which emanates from the brain for that purpose passes off without effect. The whole body feels heavy like lead. This is the last thing noticed, and soon afterwards the individual sinks into a profound sleep.

The sleep due to morphia cannot, except in its first stage, be distinguished from ordinary sleep if the dose of the alkaloid does not exceed the moderate one above mentioned. The breathing and the circulation are tranquil ; if shouted to, the individual at first gives at most some murmured

response; active stimulation produces a movement of the limbs; with continuous shaking and when called by name he will open his eyes. Other symptoms now arise if we inject into the sleeper a second and a third centigramme of the salt. After a few minutes the abdominal movements indicate that vomiting is impending, though this is not always the case. The face becomes pale, drops of perspiration appear on the forehead, the stomach is emptied, causing severe choking, whilst with the head inclined to one side the passive angle of the mouth serves as an outlet. Were we to continue the injection, the symptoms in a few hours would change again. The skin becomes cool, the temperature—taken in the rectum—falls far below the daily minimum; the pupils, when the eyelids are quickly opened, are the size of a pin's head, and remain motionless when shaded; respiration becomes less frequent, each breath is long, and becomes gradually weaker and scarcely noticeable; the pulse is hardly perceptible, slows down to from 30 to 40 beats in the minute and becomes irregular; the sounds of the heart are indistinct. The face and hands present a cyanotic appearance, every reflex act is wanting; the body lies motionless in every position, merely acting under the law of gravity like that of a dead person. The temperature falls lower and lower; mucus collects in the bronchial tubes, and as it cannot be expelled, causes a rattling and obstructs the already scanty interchange of gases. The cyanosis increases, the pulse and respiration diminish in frequency, and thus with a gradual cessation of these two vital movements death takes place quietly. Sometimes there is a twitching of some group of muscles; this, however, is not the rule, for in spite of the blood being largely charged with carbonic acid, true convulsions arising from suffocation are, for the most part, impossible, on account of the motor centres being paralysed. If we investigate in detail the specific and paralysing actions of morphine we find that they occur in the following order:—First of all the centres in the brain of consciousness and voluntary movement are paralysed, then the reflex action of the spinal cord is abolished, the respiratory centre is next affected, and finally the heart.

A good deal has been advanced with regard to the direct action of morphine upon the vaso-motor centre, and to this sleep has been attributed. Contraction of the cerebral vessels, and consequent diminished supply of blood to the brain, were supposed to be the cause of this morphine sleep. This, however, has not been established; and, as regards the heart, an individual may be sleeping soundly under the influence of morphine without that organ showing the slightest change in its action. This has also been demonstrated by sphygmographic tracings which were taken after injections of from ·01 to ·03 gramme.[1] Observant physicians are well acquainted with this, and so have no hesitation in giving morphine to patients who are suffering from heart disease if sleeplessness and mental excitement make it desirable.

A dose of morphine which speedily induces sound sleep in a healthy man, has hardly any soporific effect when subcutaneously injected into a dog, rabbit or frog. With regard to these remarkable differences, all we can say at present is, that it is only in man that the protoplasm of the brain cells responds to these small doses of morphine, or has its activity temporarily suspended by them. When morphine is given to cats it causes them to rush about in wild excitement, and this is accompanied with salivation, outstretched claws, protruding eyes, and general convulsions. In dogs death takes place after a large dose, generally with convulsions, preceded by a deep sleep.

I can easily demonstrate to you by an experiment the lowering effect of morphine on the respiratory centre. A healthy rabbit, weighing about 1500 grammes, upon which tracheotomy has been performed, is here placed on the table. In the trachea is a tube with an easily acting valve, which is connected with a meter for measuring the air, the dial-plate of which readily indicates differences of 5 c.c.; a second tube with a valve is so arranged that the inspired air can enter freely and the expired air alone pass through the meter. Whilst the animal is completely

[1] Riegel and Preisendörfer, 'Arch. f. klin. Med.,' 1878, Bd. xxv, s. 40; Frenkel and Sahli, ibid., 1890, Bd. xlvi, s. 542.

at rest we note the quantity of air expired in thirty seconds, and obtain the following results:

230—200—220—200—210—200—210 c.c.

Almost immediately after the injection of ·01 gramme (·15 grain) of morphine hydrochlorate into the jugular vein we observe a slower motion of the index, and read off—

90—100—80—90—90—90—90 c.c.

The volume of air expired is considerably reduced by means of the morphine. The dose might easily be increased without danger to the animal. This experiment shows that the irritability of the respiratory centre is lowered by morphine. Experiments on man[1] give the same results. In these experiments carbonic acid, which acts as a respiratory stimulant, was mixed with the inspired air. This gas increases the depth of inspiration, and therefore the volume of air inspired. This effect is prevented by morphine.

It has long been known that sluggishness of the bowels and constipation are caused by small doses of morphine. Colicky pains and diarrhœa are lessened by its use. It was natural to assume that morphine diminished the sensitiveness of the organ with which it was brought directly in contact, and so produced a quieting effect. Nothnagel[2] suggests that its action depends upon a stimulation of the splanchnic, the inhibitory nerve of the intestines.

Recent investigations[3] on warm-blooded animals have yielded the following results. Morphine was injected into an intestinal loop of a rabbit, and shortly afterwards the vagus, the intestinal motor nerve, was stimulated by galvanism. Movement was visible everywhere except in the loop with which the morphine had been brought directly in contact. Further, the two splanchnic nerves were cut through, and morphine was injected either subcutaneously or into the veins, and the vagus was then stimulated. The

[1] A. Loewy, 'Arch. f. d. ges. Physiol.,' 1890, Bd. xlvii, s. 601.

[2] Nothnagel, 'Arch. f. pathol. Anat.,' 1882, Bd. lxxxix, s. 1; A. Bokai, 'Arch. f. exper. Pathol. u. Pharm.,' 1887, Bd. xxiii, s. 414.

[3] Jacobi, 'Arch. f. exper. Path. u. Pharm.,' 1891, Bd. xxix, s. 171; T. Pohl, ibid., 1894, Bd. xxxiv, s. 87.

result was that no movement of the intestines took place, though the inhibitory nerves were no longer in connection with them, and even on the tenth day after section of the splanchnic on both sides, morphine checked the movement of the intestinal canal.

From this it is clear that the constipating effect of morphia, with which we are here chiefly concerned, depends on a diminished excitability of some mechanism situated in the intestinal wall.

The SECRETIONS are somewhat affected by morphine: in man small doses sometimes stimulate the salivary secretion; more frequently however, they cause dryness of the mouth: this latter effect corresponds with what has been observed, in animals at least, on the mucous membrane of the air-passages. Rossbach[1] found the following appearances on exposing the inner surface of the trachea: a quarter of an hour after injecting morphia subcutaneously the secretion of mucus had diminished fivefold. In animals, after the secretion of the mucous membrane has been thoroughly removed, about twenty seconds normally elapse before the membrane is again completely moistened by the secretion; after morphia has been injected, at least from eighty to one hundred seconds elapse before there is the same amount of secretion.

As regards THE SKIN; in the first place the sense of locality, or the power to distinguish separately the points of a pair of compasses at the minimum distance in different parts of the skin, is everywhere decreased. This begins a few minutes after the subcutaneous injection of 0·01 gramme; in the course of an hour perhaps it has reached its greatest intensity, and even after twenty-four hours the skin may still not have completely recovered itself.[2] Later an effect is produced differing from that which takes place with regard to the bronchial mucous membrane; there is increased secretion of perspiration. The skin, previously harsh and dry to the touch, becomes soft and moist.

[1] Rossbach, 'Ueber die Schleimbildung und die Behandlung der Schleimhauterkrankungen der Luftwege,' Leipzig, 1882, s. 47.

[2] Rumpf, 'Ueber die Einwirkung der Narcotica auf den Raumsinn der Haut. Verhandl. des med. Congresses,' Wiesbaden, 1883, s. 302.

Another and an undesirable accompaniment of the effect of morphine on the skin is an intolerable itching, spreading sometimes over the whole body, occurring even from medicinal doses, and occasionally accompanied by cutaneous eruptions;[1] both cease when the morphine is discontinued.

In experiments on dogs it was found that the quantity of bile secreted was not changed.[2]

The TEMPERATURE of human beings, in either a healthy or a febrile state, is not affected by morphine taken in ordinary doses. Large doses lower the temperature. This occurs even when the heart and lungs are still acting satisfactorily. The more complete the narcosis, the more sudden the fall. It seems to depend upon paralysis of the thermogenetic nerve-centres,[3] and especially upon defective innervation of the large muscles.

The difference in the action of morphine and opium—a fact which is well known to physicians—is partly explained by their chemical composition. So far eighteen alkaloids have been extracted from opium; they exist in it of course in very variable quantities, none being present in a greater proportion than 1 per cent. with the exception of morphine and narcotine. NARCOTINE may amount to 8 per cent.; its formula is $C_{22}H_{23}NO_7$. Next to it comes THEBAINE, of which opium contains 0·5 per cent.; its formula is $C_{19}H_{21}NO_3$. The action of both of these substances on animals is altogether different from that of morphine.

To demonstrate this I will take THEBAINE, as it is more soluble than narcotine. I inject into a healthy frog one centigramme of thebaine dissolved in a cubic centimetre of water acidulated with hydrochloric acid. Had I injected one centigramme of hydrochlorate of morphine no effect would have been produced beyond the initial irritation caused by the slight pain of the injection. It is different,

[1] Möbius, 'Berliner klin. Wochenschr.,' 1882, s. 707.

[2] Rutherford, 'Transactions of the Royal Society,' Edinburgh, 1879, vol. xxix, p. 232.

[3] J. Rückert, 'Einfluss des Morphins auf die Temperatur einiger Warmblüter,' 1882; R. Gottlieb, 'Arch. für exper. Path. und Pharmak.,' 1890, Bd. xxvi, s. 429.

however, after injecting the thebaine. In a few minutes the frog becomes restless, as though he were seeking some easy position. Twitchings of the limbs and, on my shaking the table, general tetanic spasms are produced. On decapitating the animal the spasms do not cease, but continue for a time, though growing gradually weaker with the death of the spinal cord from which they obviously arise. On exposing the heart it is seen to beat forcibly, and if we investigate the effect of thebaine on this organ alone in warm-blooded animals, it can be shown[1] that the frequency of the pulse is considerably increased, and the blood-pressure raised, in consequence of the stimulation of the heart and of the vaso-motor centre. Convulsions, arising from irritation of the spinal cord, also occur in warm-blooded animals. Pigeons, which are almost immune from the effect of morphine, are acted upon most violently by one centigramme of thebaine.

This experiment is merely to show you the great difference which exists among the alkaloids of opium with respect to their mode of action. In the case of man they would present similar differences; an exact proof, however, of this has not yet been furnished. Efforts have frequently been made in this direction, but so far not with marked success. The unreliability of the preparations employed may have been one of the causes of failure.

A recent work[2] on this subject says: "In codeine, papaverine, narcotine and thebaine, which are derived from morphine by the substitution of alcoholic radicals, the narcotic effect of morphine is diminished, whilst the tendency to induce spasm is increased.

From all this it is obvious that in prescribing opium the physician administers a complicated body producing secondary effects which cannot be regulated, depending as they do on the varying proportion of the alkaloids contained in the opium. He should therefore never prescribe it where the conditions are urgent, and where the object is to pro-

[1] J. Ott, two reprints from the 'Boston Med. and Surg. Journ.,' without date.

[2] W. von Schröder, 'Archiv f. exper. Pathol. u. Pharmak.,' 1883, Bd. xvii, s. 96.

duce rapidly and decisively the special action which morphia possesses.

Extractum Opii is a simple preparation. It is a reddish-brown substance, soluble but forming a turbid solution in water, and is prepared by macerating opium in water, and evaporating the liquid; it contains morphine, but is free from several of the other alkaloids which are either insoluble or only slightly soluble in water. The maximum dose, like that of opium, is 0·15 gramme (2·25 grains).

Tinctura Opii Simplex (Tinctura Thebaica).—This is chiefly an aqueous, but partly an alcoholic extract of powdered opium; it is of a reddish-brown colour, and has the smell and bitter taste of opium. 100 grammes of the tincture contain the soluble portion of 10 grammes of opium, or approximately 1·0 gramme of morphine.[1]

Tinctura Opii Crocata (Laudanum liquidum Sydenhami).—This is prepared from powdered opium, saffron, cloves, cinnamon and proof spirit; it contains the same alkaloids as the previous tincture. Of a dark yellowish-red colour, it has a bitter taste and the odour of saffron. The essential oils are present in so small an amount that their effect is unimportant. The dose of both the above tinctures is from 0·3 to 1·5 c.c. (5 to 25 minims).

Tinctura Opii Benzoica[2] (Elixir Paregoricum).—This is prepared from opium, benzoic acid, camphor, oil of aniseed and proof spirit. It is of a brownish-yellow colour, has the odour of aniseed and camphor, a strongly aromatic and sweetish taste, and an acid reaction. The effect of the small amount of benzoic acid in an ordinary dose of the tincture hardly requires consideration. The amount of morphine in it is twenty times less than in the two other tinctures.[3] From thirty to sixty drops may be prescribed several times a day; it is best taken alone.

Dover's powder (Pulvis Ipecacuanhæ Opiatus), consisting

[1] Tinctura Opii ('Ph. Brit.') in 100 parts contains the soluble portion of 7·5 parts of opium, or about 0·75 per cent. of morphine (translator).

[2] Similar to Tinctura Camphoræ Composita ('Ph. Brit.'), but stronger (transl.).

[3] Tinct. Opii ('Ph. Brit.') contains fourteen times more morphine than Tinct. Camph. Comp. ('Ph. Brit.')—transl.

of one part of opium, one part of ipecacuanha and eight parts of sugar of milk,[1] must be considered as having essentially the same effect as pure opium, so long as we are without proof that the slight addition of emetine modifies or corrects the effects of the alkaloids.

Codeine (from ἡ κώδη, the poppy head), formerly a medicinal alkaloid, has now been superseded in practice by Codeinum Phosphoricum, the latter being more stable and possessing better-marked characters; it appears in the form of fine white needles, having a bitter taste, easily soluble in water, less so in alcohol. The watery solution has a slightly acid reaction. The formula of codeine is $C_{17}H_{18}NO_2.OCH_3$, methyl-morphine, that is, morphine in which one atom of hydrogen is replaced by the radical methyl. The medicinal salt contains in addition one molecule of H_3PO_4, and two molecules of water of crystallisation.

The experiments hitherto made on animals do not allow any direct inference to be drawn as to the effect of codeine on man.

The alkaloid acts differently on different species of animals, and there is no substantial agreement among the experimenters as to their results. As I have before hinted, this may be owing to the use of preparations which are not absolutely pure. Consequently we must be guided by the results of clinical experience, choosing those data which appear to be the most reliable.

Codeine is said to act as a specific in quieting that portion of the sympathetic which is in connection with the abdominal viscera, and to do this without interfering with the activity of the intestines. This holds good for all painful affections of the intestines or ovaries. Further, it is of service in the tormenting cough associated with phthisical mischief, as well as in bronchial affections generally, when the secretion is not excessive, and in sleeplessness when this is not brought about by severe pain. Moreover it does not give rise to any unpleasant collateral effects. It does not interfere with the peristaltic action of the intestines or produce mental confusion, nor does it induce a craving for constantly repeated doses.

[1] Replacing potassium sulphate in the Pulvis Ipecac. Comp., 'Ph. Brit.' (transl.).

At the same time poisonous results have been produced by too large a dose. A child of two years old had 0·1 gramme (1·5 grains) given to it in the course of a few hours. The following symptoms are said to have been produced :—a death-like pallor, coldness of the limbs, the pulse and heart-beat imperceptible, the abdomen distended, the eyes fixed and staring with widely dilated pupils, and dryness of the mucous membranes. Stimulants were administered, and after a few hours the child rallied.[1]

The dose of phosphate of codeine is about three times that of hydrochlorate of morphine. From 3 to 6 cg. ($\frac{1}{6}$ to $\frac{1}{3}$ of a grain) may be administered two or three times a day with advantage. The German Pharmacopœia has fixed 0·1 gramme (1·5 grains) as the maximum single dose, and 0·4 gramme (6 grains) as the maximum quantity to be given in twenty-four hours.

Opium, especially when administered in the solid form by the mouth, has an uncertain action on the brain; this mode of administration is only applicable, in a general way, when it is desirable to influence the intestinal tract. The administration of morphine by the mouth has in most cases for

[1] The following works on the subject may be consulted:—Barbier, 'Gaz. méd. de Paris,' 1834, s. 147; Berthé, 'Mon. d. hôpit.,' Paris, 1856, ss. 4, 596, 601, 692; Lauder Brunton, 'Brit. Med. Journ.,' 9th Jan., 1888; Fischer, 'Corr.-Bl. f. Schweizer Aerzte,' 1888, No. 19; Dornblüth, 'Therap. Monatshefte,' 1889, s. 363; G. Rheiner, ibid., ss. 393 u. 456; H. W. Freund, ibid., s. 399; W. v. Schroeder, loc. cit., s. 111; Kobler, 'Wien. med. Wochenschr.,' 1880, No. 12; Loewenmeyer, 'Deutsche med. Wochenschr.,' 1890, No. 20.

nearly thirty years been superseded by its injection under the skin, and in the practice of the present day hypodermic or subcutaneous injections play an important part.

For a long time back frequent attempts were made [1] to administer powerful remedies in some other way than by the intestines, but none of the various methods proved reliable and practicable.

In 1855 A. Wood[2] in Edinburgh directed attention to the fact that the syringe and tubular needle constructed by Pravaz and Fergusson, and used by surgeons to inject astringent fluids into aneurisms and nævi, might be successfully employed for the introduction of easily soluble preparations of opium under the skin. Five years elapsed before the new method was established in Germany; it owed its complete success at last to a somewhat lengthy treatise by v. Graefe,[3] who pointed out its great value in ophthalmic practice. Since that time it has brought much relief to suffering humanity, but its use has also been attended with some drawbacks. Let us consider now more closely the advantages and disadvantages of this method, especially as regards the administration of morphia; for the amount of any other drug that is subcutaneously injected is absolutely insignificant in comparison with what is used of this substance.

I will simply mention cases in which there is some pathological or purely mechanical obstruction to the administration of morphia by the mouth, and such cases also as are accompanied by obstinate vomiting and purging. Formerly in these cases the physician was perfectly helpless, even where with the use of morphine life might have been saved.

There are no difficulties in, or obstacles to, the injection of morphine under the skin unless the patient has a marked hæmorrhagic tendency.

The stomach and intestines are less affected locally by the hypodermic use of the alkaloid; given in this way it does not interfere with the appetite, nor does it so easily or

[1] For details consult Eulenburg, "Percutane, intracutane, und subcutane Arzneiapplication," in v. Ziemssen's 'Allgem. Therapie,' 1880, Bd. i, Tl. 3.

[2] A. Wood, 'Edinb. Med. and Surg. Journal,' 1855, vol. lxxxii, p. 265.

[3] v. Graefe, 'Archiv für Ophthalmologie,' 1863, Bd. ix, s. 62.

so readily occasion constipation, both of which points are of the greatest importance in the treatment of many disorders.

Its soothing effect upon the brain is rapid and certain. We know that within ten minutes at most, after the injection of 0·01 gramme ($\frac{1}{7}$ of a grain) of hydrochlorate of morphine, refreshing sleep will as a rule be induced. The numerous lymphatic vessels of the skin readily absorb the morphine solution, the absorption being promoted by the pressure due to the skin's elasticity, and convey it to the nervous centres. Apart from the fact that in the coats of the stomach the absorbent vessels do not come in such direct contact with the fluid as they do under the skin, the chances of their being already filled with fluid or of their being in an unhealthy condition must be taken into account.

It was on a memorable occasion that I first had extensive personal experience of the great advantages attendant on this method of administering the remedy. On the evening of the 16th of August, 1870, after the battle of Rezonville, near Metz, I undertook the charge of over 180 soldiers who had been wounded, half of them severely, and admitted them into my field-hospital, the church of Gorze, which had been utilised for that purpose. The men were driven up to the flight of steps outside the church in ambulance waggons; here they had to be lifted out, carried up the steps on stretchers, and laid on beds of straw in the church. In anticipation of the amount of suffering which would be attendant upon their removal from the waggons, and their carriage up the steps and to their beds, I had 200 c.c. of a 1 per cent. solution of morphine prepared. Before any wounded man was lifted out of the ambulance he had a syringeful (1 c.c.), or if needful a syringeful and a half of the solution subcutaneously injected.

Ten minutes were allowed to elapse, and then each man was lifted up and carried to his bed in the church. The result of these injections was that no cry of distress was heard, and that the first night, which to wounded men is probably the most painful, was passed in complete repose. In any case they were not exhausted by pain, and thereby much of their recuperative power was preserved; this could not have been done by prescribing morphia in the old fashion.

Isolated cases of a similar nature must have been observed by every physician, nor as yet can we hope that their collective occurrence will, in the future, be spared to humanity.

It seemed probable that morphine might have a local action on peripheral nerves which had become tender and sensitive. Experience teaches us that in those organs with which the lymphatic vessels of the skin are in direct communication, pain may be quickly relieved or removed by subcutaneous injections. It almost appears as though the morphine acted directly on the painful part without being first carried to the brain,—that is, without influencing or depressing the central sensory nerve-cells. This led von Graefe to advise that the spot where the injection was to be made should be carefully considered, and in spasm of the eyelids, for example, that the tender points—"points douloureux"—of the sensory nerves should be found, and the injection made near these. Other authors have spoken highly of the local effect on other organs. A case of paralysis affecting both sides is reported,[1] in which invariably, remission of pain only took place on that side in which the injection had been made close to the seat of pain. A very similar case was also observed by Eulenburg, and Schüle[2] reports the case of a patient who was subject to attacks of mania, following upon an injury to his head, in whom impending attacks could only be warded off by subcutaneous injections in the neck close to the wound.

Nevertheless the matter is not quite so simple as it appears at first sight. There are cases where no such local effect is produced, and the experiments on healthy individuals have even been followed by contrary results. Even pure water when injected subcutaneously can diminish the sensitiveness of the part. I may here refer to the experiments of Jolly and Hilsman.[3] They tested the sensitiveness of the skin to a faradic current of corresponding points on the

[1] Sommerbrodt, 'Wien. med. Presse,' 1865, No. 46 (nach Eulenburg).

[2] Schüle, "Geisteskrankheiten," in v. Ziemssen's 'Spec. Path. u. Therapie,' 1878, s. 667.

[3] Hilsman, 'Doctordissertation,' Strasburg, 1874; also Jolly, 'Archiv f. Psychiatrie,' 1877, Bd. viii, s. 215; Rumpf, loc. cit., "Ueber die Herabsetzung des Raumsinns der Haut." An opposite view is advanced by Eulenburg, loc. cit., p. 69.

two sides in the following manner:—the current from a secondary coil was conducted to the skin through two knitting-needles a centimetre apart, fastened in a piece of cork, and then on approximating the secondary coil to the primary, they noted at which graduated division on the rod the current was first felt. So soon as the remedy caused diminished sensitiveness to pain, both sides seemed always to be equally affected; the morphia appeared to diminish the sensitiveness of the skin simply through the nervous centres. However this may be, we shall for the present do best, as far as practice is concerned, by acting as follows. If on account of peripheral irritation it is necessary to inject morphine subcutaneously, we must have regard to the positive results in relieving local irritation which have been obtained clinically, and choose a point as near as possible to the affected part for the injection, especially if we know that by means of the lymphatics this portion of the skin is in direct communication with the affected part.

For obvious reasons an injection should never be made in the neighbourhood of large vessels or superficial nerve-trunks. Especial caution, too, must be exercised with regard to the quantity administered, for absorption takes place so rapidly that the activity of the remedy is materially increased. At the time when the hypodermic injection of morphine first came into use, cases were reported of patients fainting immediately after the injection and remaining unconscious for hours. In these cases either the precaution above mentioned had been disregarded, or some mistake had been made as to the dose of morphine, and possibly five to ten times too much had been administered.

The calculation of the dose is rendered easy and safe if we use a syringe holding exactly a gramme (15 minims) of water, and a solution containing one per cent. of morphine. Even if the entire contents of the syringe are injected at once (=0·01 gramme or $\frac{1}{7}$ of a grain of morphine) no bad effects can be produced, except perhaps in children; to these morphine should not be administered at all, or only after most careful consideration of the dose, because of their great susceptibility to this drug, a susceptibility specially marked in the case of infants under one year.

The use of morphine subcutaneously has its drawbacks. It may easily give rise to a craving for morphine, and develop the morphine habit.

If a patient after being racked with pain has frequently, at short intervals, experienced the ease and comfort afforded by morphine, he soon begins to beg and entreat that the dose may be repeated, and as a result the seductive and soothing influence of the drug becomes a daily necessity to his nervous system. With ever-growing excitement and with feverish expectation he longs for the hour when the injection is to be made; and if, as is unfortunately frequently the case, drug and instrument are at hand, he does not even wait till then. Each day almost an increased dose is injected, for the nervous system soon becomes tolerant of the stimulus, and larger doses must be taken to induce repose. Sleeplessness, trembling of the limbs, sexual impotence, general restlessness, palpitation of the heart, complete disappearance of hydrochloric acid in the stomach, loss of appetite, nausea, intermittent febrile attacks, saccharine diabetes, wasting of the testicles or ovaries,[1] and failure of power, are some of the consequences of continuous indulgence in morphine. If the habit is persisted in the patient falls into premature decay. The only successful way of checking the habit is for the patient to place himself in some institution where sudden or gradual abstention from the poison may be carried out under careful supervision.[2]

The most marked symptoms resulting from the sudden deprivation of the drug are cerebral excitement, extreme restlessness in all the muscles, pain in the stomach, and, associated with this, a burning sensation in the back.

Hence it follows that it is only under two conditions that the physician is justified in administering injections of mor-

[1] W. Levinstein, 'Centr. f. Gynäkologie,' 1887, ss. 633 und 841.

[2] R. Burkart, "Zur Pathologie der chron. Morphiumvergiftung," 'Deutsche med. Wochenschr.,' 1883, s. 33; 'Sammlung klin. Vorträge,' 1884, No. 237. Special reference may be made to the monograph of A. Erlenmeyer, 'Die Morphiumsucht und ihre Behandlung,' 3 Aufl., 1887. The author here, on pages 92 and 422, controverts views which he attributes to me, which, however, I have never maintained nor even suggested.

phine : (1) when, in the treatment of an acute disorder, one or a few injections only will probably be required ; and (2) when the morphine craving, if developed, would be a lesser evil than to allow the patient to suffer the pain and excitement which can be subdued by the drug. To the first category belong recent wounds, acute neuralgias, and sleeplessness in acute illness, which leads to consequent failure of strength. To the second belong cancer, tuberculosis, incurable neuralgias, and the like.

When the death agony is accompanied by severe pain the injection of morphine is also specially indicated. Continuous neuralgic pain exhausts the strength more quickly than a carefully adjusted dose of morphine, and it evinces but a slight grasp of the position as well as weak logic if physicians in such cases, with a sort of holy horror, withhold from the unhappy patient the most soothing remedy they can give ; while, as if to rally the vital powers of the patient, and once more to restore him to a complete sense of his hopeless condition, they supply him with one stimulant after another.

A work [1] has been published on the more immediate cause of the morphine habit, and the strange subsidence of its acute symptoms on renewing the injections of morphine.

The conclusion arrived at is that in chronic poisoning an acrid and irritating substance is produced from the tranquillising morphine, termed oxydimorphine—

$$2C_{17}H_{19}NO_3 + O = C_{34}H_{36}N_2O_6 + H_2O,$$

the effects of which upon the tissue-cells is again neutralised by fresh doses of morphine.

Against this explanation it is alleged that the symptoms said to be due to the discontinuance of the morphine may only appear long after its use has been abandoned—at a time, that is to say, when the oxydimorphine, which is quickly excreted, no longer exists in the system. Symptoms not unlike those referred to above sometimes appear after the sudden withdrawal of some other stimulant which has been habitually indulged in. These symptoms

[1] W. Marmé, 'D. med. Wochensch.,' 1883, s. 197 ; Polstorff, 'Ber. d. D. chem. Ges.,' 1880, s. 86.

are probably referable to that reaction which is so often noticed in nerve-life, and which is developed by the continuous absence of what has become a necessary stimulant.

A portion of the morphine is probably oxidised in the system. Very little is found in the urine, for after as much as 1·5 grammes (23 grains) have been subcutaneously injected within forty-eight hours into a patient suffering from the morphine habit, no trace was found in the urine. It seems that most of it is excreted from the blood by the mucous membrane of the stomach, and thence gradually passes into the intestines and is discharged with the fæces.[1]

It was generally supposed that the stomach was very little affected by subcutaneous injections of morphine. The contrary, however, has been experimentally demonstrated. After injections of this kind morphine was excreted into the stomach; the excretion began in from two to three minutes, continued distinctly for half an hour, then diminished in a marked degree, and ceased entirely after about fifty or sixty minutes. The tendency to vomit after subcutaneous injection did not occur till after the morphine had been already excreted into the stomach, and was obviated by washing out the stomach. It was estimated that the amount of the alkaloid excreted was about one half of that injected. The poisonous action (in dogs) was materially lessened by frequently washing out the stomach. In this way doses which otherwise would have been certainly fatal were rendered harmless.

Three healthy young men had each 3 cg. (0·46 grain) of morphine subcutaneously injected. In all three cases morphine appeared in the stomach, which had previously been well washed out. It could be detected in the stomach in two and a half minutes after the injection; at the end of forty minutes traces were still discernible, but after an hour there was no further evidence of its presence. In none of the cases was there any noticeable effect of morphine on the system. One of those experimented upon, an attendant in

[1] On this point compare E. Landsberg, 'Archiv f. d. ges. Physiol.,' 1888, Bd. xxiii, s. 413; J. Donath, ibid., 1886, Bd. xxxviii, s. 528; J. Donath, 'Journ. f. prakt. Chemie,' 1886, Bd. xxxiii, s. 595; E. Tauber, 'Archiv f. exper. Path. u. Pharmak.,' 1890, Bd. xxvii, s. 336.

the Clinic for Nervous Diseases at Halle, did not even discontinue his work.[1]

"Moderate and full" doses of morphine administered to nursing mothers in no case produced injurious effects on the infant; long and deep sleep sometimes followed,[2] which, however, in the case of healthy infants is not unusual, even without morphine. In other experiments from 3 to 6 cg. (about ½ a grain to a grain) of morphine were administered during the twenty-four hours to wet-nurses without any perceptible effect on the infant. On making a chemical analysis of the milk no morphine could be detected.[3] The accuracy, however, of these statements has been called in question.[4]

In the East the watery extract of opium is largely used for smoking, the smoke being inhaled into the lungs as deeply as possible. It has been denied that any of the injurious effects so often described as arising from this practice ever do occur, and opium smoking has been strongly recommended for all kinds of nervous disorders.[5]

The use to which morphine can be advantageously employed at the bedside is so varied, that it is only from the clinical standpoint that the details can be properly studied.

We have here, however, to consider what are the characteristics of the pure preparations of morphine; a knowledge of them is important because this expensive drug is sold not unfrequently in an adulterated condition.

[1] Hitzig und K. Alt, 'Berl. klin. Wochensch.,' 1889, s. 560.

[2] Fehling, 'Centralb. für Gynäkol.,' 1884, s. 659.

[3] Pinzani (Bologna), 'Wiener med. Wochenschr.,' 1880, s. 157.

[4] Fubini, ref. 'Cbl. f. klin. Med.,' 1890, s. 729; Fubini und Cantu, Moleschott's 'Unters. z. Naturlehre,' 1891, Bd. xiv, s. 396; Fürst, 'Centralbl. f. klin. Med.,' 1891, s. 73.

[5] Thudichum, 'Verhandl. d. Congr. f. innere Med.,' 1883, s. 307.

Such an occurrence took place in Berlin in 1866, when it was found that the morphine supplied to the medical stores of an entire division of the army was adulterated.

The preparations used are the acetate, hydrochlorate and sulphate of morphine.

The use of the acetate of morphine, which was chiefly employed formerly, has now been almost entirely abandoned. Owing to the instability of the acid a salt is soon formed which contains a larger proportion of alkaloid than at first, and which, moreover, is not easily soluble in water. Let us examine the contents of this glass containing acetate of morphine; it has a strong odour of acetic acid. The composition, however, of powerful and active remedies ought to undergo no change.

Hydrochlorate of morphine has the crystalline prismatic form I have already shown you. It dissolves in twenty-four parts of water at 15° C. (59° F.), and has a distinctly bitter taste. The following are, among others, the reactions by which it may be identified. I place in a flat porcelain dish as much morphine as will lie on the point of a penknife, and pour over it about 10 c.c. of a solution of sesquichloride of iron, which has been diluted until it has a straw-coloured tint; the morphine and the whole mixture immediately assume a greenish-blue colour. A similar quantity is now placed in a test-tube, to which a few cubic centimetres of pure concentrated sulphuric acid are added, and then gently heated. The acid now must not turn yellow, or only very slightly so; on cooling and then adding a few drops of nitric acid the solution assumes a beautiful purple-red colour. The second test determines the presence or absence in the morphine of such things as starch, sugar, &c.; when warmed with sulphuric acid these substances immediately develop a brownish or black colour.

A test which may be employed to detect the presence of mineral substances, such as baryta, alumina, &c., in any of the pharmacopœial salts of the alkaloids, is to incinerate them on platinum-foil (or the blade of a knife); the salt must be completely dissipated; if any mineral substance is present it will remain behind.

There exists in opium and its preparations a peculiar acid

by means of which the drug may be chemically identified. This is meconic acid; it crystallises in mica-like plates, and has the formula $C_7H_4O_7$. It is chiefly in combination with this that the morphine exists in opium. If a solution of sesquichloride of iron is added to an aqueous solution of this, it assumes a deep red colour, which is not destroyed on the addition of hydrochloric acid (thus differing from the colour produced by the action of Fe_2Cl_6 on acetates), nor by mercuric chloride (thus differing from the colour produced by the action of this reagent upon the sulphocyanides).

Extract of opium and tinctures of opium give the same reaction, of course not so distinctly as is the case with the separated meconic acid.

Meconic acid produces no special effects on the system. Opium and its simple tincture can also be identified by the odour, which is somewhat characteristic. It is still sometimes called narcotic; the word is misapplied, for *ναρκάω* means "I stupefy," and, as far as I know, no one ever yet was stupefied by the odour of opium. Of the odour itself nothing further is known.

Opium or morphine administered internally almost always gives rise to constipation of the bowels; morphine itself often causes vomiting or nausea, especially in anæmic persons, sometimes also itching and eruptions of the skin. Owing to these drawbacks a substitute which possesses the pleasant soporific effects of morphine without its attendant discomforts has long been sought for. In long illnesses morphine loses its tranquillising effect, and a change to some other soporific is necessary. Various substances have been tried; among those of less recent introduction the most important and interesting is INDIAN HEMP, the drug known in the north of India under the name of Bhang or

Gunjah, which is the dried tops after flowering of the female plants of CANNABIS SATIVA, gathered before the seeds are ripe, and from which the resin has not been removed, or it is made up of the scabrous and downy leaves and capsules. Formerly the officinal name of the plant was Herba Cannabis Indicæ.

Hemp and its preparations form an important element in the lives of Orientals. They have long been familiar with its soporific and inebriating effects, the latter usually of an agreeable or cheerful character. Many accounts have been given of its effects, in which truth and fiction have been strangely mingled.

It is much used either in the form of Churrus, the resinous exudation of the hemp ; or the resinous product is mixed with sweetmeats, or made up as an electuary with aromatics, or made with gum tragacanth into small pastilles. The drug is either swallowed or smoked. The general term for all preparations of Indian hemp is Haschisch. By means of it the impressionable and imaginative Oriental enjoys the bliss of paradise, and even the sober Teuton under its influence passes into the land of dreams and visions.

Schroff[1] gives the following description of its effects from his own personal experience :—At 10 p.m. I took 7 cg. (one grain) of dried haschisch and got into bed. I read some indifferent literature, smoking a cigar according to my usual habit until 11 o'clock. I then composed myself for sleep with the impression that the dose had probably been too small, as it had produced no effect upon me, and my pulse was unaltered. Immediately, however, I experienced a loud rushing sound, not only in my ears but all over the head. It was extremely like the noise of boiling water; simultaneously I was surrounded with an agreeable brightness, which seemed to permeate my whole body and to render it transparent. With unusual facility a whole series of ideas, exalted and refined in character, passed through my mind ; I regretted having no writing materials at hand, so as to note down these delightful experiences ; nor could I bring myself to rise and fetch them, for I was afraid to drive away the very enjoyable sensations I was then

[1] Schroff, 'Lehrbuch der Pharmacologie,' 1869, s. 500.

experiencing; and, moreover, I was fully convinced that on the following morning I should, as the ideas had been so clearly impressed upon me and the sensations were so vivid, be able easily to recall them. I recognised my condition to be that which had been described as brought about by Haschisch, but I noticed that there was an entire absence of erotic sensations. On the following morning my first thought on awaking was to bring back to my memory the vision of the past night, but of the glorious sensations I had experienced I could recall nothing beyond what I have above stated."

The dominant sensation experienced when smoking Indian hemp (the *kif* or *tekrowia* of Algeria) is a pleasing indifference to all external impressions, a sort of *bien-être;* if the habit is continued for some time further symptoms show themselves.

For a considerable time Freusberg had a young Englishman under observation who habitually dosed himself with Tinctura Cannabis Indicæ, beginning with a dose of 1·8 c.c. (about 28 drops), and gradually increasing it to 24 (about 6 drachms), 6 c.c. (a drachm and a half) being his medium dose.[1] When the patient, alone in his rooms, indulged in smoking the hemp, orchestral music, which any casual noise developed, filled his ears, and theatrical performances and dancing figures presented themselves before him. On gazing into empty space beautifully coloured landscapes, peopled with men and animals, and associated with the murmur of waterfalls and trees, and with vocal and instrumental music, charmed his senses. The music he heard was soft, every sound agreeable, without discord or harshness; the face of anyone who might enter was often distorted, the expression generally comical, never repulsive. His impressions were all characterised by freshness and vivacity, endless variety, and extraordinary combinations of various things he had seen and remembered.

It is evident that an hypnotic productive of such effects is, like the soothing φάρμακον νηπενθὲς with which Helen[2]

[1] Freusberg, 'Zeitschr. f. Psychiatrie,' 1877, Bd. xxxiv, s. 216.

[2] "Meantime, with genial joy to warm the soul,
Bright Helen mixed a mirth-inspiring bowl;

drugged the wine of Telemachus and his sorrowing companions, well adapted for use in painful disorders. It has therefore been introduced into the pharmacopœias, and in the German one both the alcoholic extract and the tincture are included as well as the plant itself. Our preparations, however, differ widely one from another, according to the locality from which they come; further, they are unstable, and owing to both these causes yield variable and untrustworthy results. Doses that in one case may act most satisfactorily in giving relief, in another will produce lassitude, nausea, vomiting, palpitation of the heart, a feeling of anxiety, and allied symptoms; and in a third, such profound narcosis as to give cause for alarm.[1]

The habitual use of preparations of hemp produces results similar to those that follow the use of opium and morphia. This is so well known in the East, that when the French occupied Egypt in 1800 they prohibited the use of hemp, on the ground that "habitual drinkers and smokers of it lose their senses, and becoming violently delirious, are led into excesses of every kind." On this account "the distillation

> Tempered with drugs of sovereign use t' assuage
> The boiling bosom of tumultuous rage;
> To clear the cloudy front of wrinkled care,
> And dry the tearful sluices of despair.
> Charmed with that virtuous draught, th' exalted mind
> All sense of woe delivers to the wind:
> Though on the blazing pile his parent lay,
> Or a loved brother groaned his life away,
> Or darling son, oppressed by ruffian force,
> Fell breathless at his feet a mangled corse;
> From morn to eve, impassive and serene,
> The man entranced would view the deathful scene.
> These drugs, so friendly to the joys of life,
> Bright Helen learned from Thon's imperial wife,
> Who swayed the sceptre where prolific Nile
> With various simples clothes the fattened soil.
> With wholesome herbage mixed, the direful bane
> Of vegetable venom taints the plain;
> From Pæon sprung, their patron-god imparts
> To all the Pharian race his healing arts."
>
> *Odyssey*, bk. iv, l. 219, *et seq.*

[1] Pusinelli, 'Deutsche med. Wochenschr.,' 1886, s. 815.

of liquors from haschisch is prohibited throughout Egypt. The doors of those coffee-houses or inns where it is supplied will be walled up, and their proprietors imprisoned for three months. All articles containing haschisch will be confiscated and publicly burnt."[1] And yet, even at the present day, the habitual indulgence in hemp is the cause of many incurable mental disorders in Egypt, Turkey and Asia. It is one of the causes that has destroyed the old warlike energy of Eastern nations.

So long as we are unable to obtain stable and active preparations of Indian hemp it has merely a scientific interest.[2] The same may be said also of LACTUCARIUM, the dried milky juice of *Lactuca virosa*, the strong-scented lettuce (Nat. Ord. Compositæ), which was at one time officinal. The following group of hypnotics recently brought into use has supplied the want that formerly existed, and in my opinion enables us to dispense with such uncertain preparations as those of Cannabis indica or Lactuca virosa.

[1] From G. Martin's 'Pharmakol. med. Studium über den Hanf.,' 1856, s. 84.

[2] On this head compare the latest publication on the subject by G. Sée, of Paris, in the 'Deutsch. med. Wochenschr.,' 1890, s. 679 ff.

V.

Chloral hydrate—Its preparation—Effect on the brain, the vascular system, the temperature, &c.—Its advantages and disadvantages—The changes it undergoes in the organism—Chloral formamide—Paraldehyde—Amylene hydrate—Sulphonal—Poisoning by morphine and chloral hydrate—Its frequency—Diagnosis and treatment—Artificial respiration—Stimulation of the heart's action—Restoration of the bodily temperature—Atropine as an antidote.

Of the various substances included in the group referred to at the close of the last lecture, CHLORAL HYDRATE is the one with which we have longest been familiar. It consists of dry, colourless, transparent crystals of the monoclinic system, which do not deliquesce on exposure to air, and which melt at 58° C. (136·4° F.). It has an aromatic odour that becomes somewhat pungent on the application of heat. The taste is slightly bitter and caustic. It is easily soluble in water, alcohol, and ether.

The composition of chloral hydrate is $C_2Cl_3OH + H_2O$. Deprived of one molecule of water it is termed chloral, which is also a colourless liquid, having a pungent odour and caustic action, and for this reason is never employed. When, for the sake of brevity, the term chloral is used in medicine it simply refers to chloral hydrate.

Chloral was first discovered by Liebig in 1832, and in 1834 its molecular formula was published by Dumas. It may be obtained by passing a continuous current of dry chlorine gas for a considerable time through anhydrous ethylic alcohol, the temperature of the latter being gradually raised to 60° C. (140° F.). The alcohol is all decomposed and the process is at an end when hydrochloric acid ceases

to be evolved. The changes which take place may substantially be represented as follows :

(1) $C_2H_5.HO + Cl_2 = CH_3.CHO + 2HCl.$
(2) $CH_3.CHO + 3Cl_2 = CCl_3.CHO + 3HCl.$

That is, the alcohol by the action of the chlorine is first converted into aldehyde, which is then, by the further displacement of three atoms of hydrogen by three of chlorine, converted into chloral.

The process, however, is not quite so simple as is indicated above. Other substitution products of chlorine are formed in small quantities, from which the chloral has subsequently to be freed. Chemically chloral is regarded as *trichlor-aldehyde*, or as the aldehyde of trichloracetic acid :— $C_2Cl_3HO_2$ or $CCl_3.COOH$.

Chloral was not employed medicinally until the year 1861, when Buchheim first tried its soporific effects on himself and on his patients. But he published no communication on the subject till 1872.[1] O. Liebreich made similar investigations in 1869, and after careful experiments introduced chloral hydrate as a most valuable remedy into general use.[2]

I have here injected subcutaneously 0·5 hydrate of chloral dissolved in 5·0 water into a medium-sized rabbit. The animal at first shows symptoms of pain, indicating that hydrate of chloral has some effect on the tissues ; this is especially the case as regards the mucous membrane of the stomach, which, when at all sensitive, does not readily tolerate the drug.

In a few minutes we perceive all the signs of impending sleep. The animal can no longer stand on its legs, which now hang loosely from the body. The head at first falls forward, and then from side to side ; and if now I place the animal on its side, it lies in this most unusual position, as if it were dead. The ocular or peripheral reflexes in general, which can otherwise be easily developed, are also abolished. Only the gentle regular breathing, and the beating of the heart, which can easily be felt against the chest wall, show us that the animal is still alive. If I now put it in a warm

[1] Buchheim, 'Archiv f. pathol. Anat.,' u. s. w., 1872, Bd. lvi, s. 2.
[2] O. Liebreich, 'Berlin. klin. Wochenschr.,' 1869, s. 325.

place, in a few hours the effects of the drug will have completely passed away.

Experiments on the dog and cat produce exactly similar results. These effects of chloral, corresponding so completely with what is observed in man, justify us in studying its further action on animals, and it has thus been proved that chloral, differing in this respect from the action of morphia, very soon affects the VASCULAR SYSTEM. The blood-pressure is lowered[1] and the walls of the arteries relaxed; the heart, however, continues to beat vigorously—of course I am still referring to full narcotic doses, and not to poisonous ones; the diminished blood-pressure must therefore be chiefly dependent upon the diminished vaso-motor contraction of the vessels. The sphygmographic tracings obtained from experiments on man[2] corroborate this; the tension of the radial artery is considerably diminished, the frequency of the pulse remaining almost unchanged, though after a time this also may be lowered. The weakening of the vaso-motor nerves is further demonstrated by the diminished irritability of their centres. Usually, when a sensitive nerve is stimulated, the blood-pressure, owing to the contraction of the arteries, is at once considerably increased; but if chloral has been previously administered the reaction is less, and may even be altogether absent.

The ordinary dose which induces sleep will also lower the TEMPERATURE from 0·2° to 1° C. (0·36° to 1·8° F.). This is chiefly due to the dilatation of the vessels of the skin; more heat is thus dissipated into the surrounding air. This, however, is not the sole cause, for Hammarsten[3] found that the temperature of animals when well wrapped in wadding was still reduced after taking chloral. Consequently there must be a diminished production of heat, and we must therefore take into consideration here, as with morphine, the diminished tone of the large muscles of the body and limbs, and the lowered activity of other cells in the organism. The sleep produced by chloral is not different in man from what you see here in the rabbit. In both, if too strong a dose

[1] Heidenhain, 'Archiv f. d. ges. Physiol.,' 1871, Bd. iv, s. 557.

[2] Preisendörfer und Riegel, 'Archiv f. klin. Med.,' 1879, Bd. xxv, s. 40.

[3] Hammarsten, 'Deutsche Klinik,' 1870, ss. 417, 434, 446, 462.

is taken, in the former case from 5 to 10 grammes (75 to 150 grains), in the other from 1 to 3 grammes (15 to 45 grains), the sleep becomes more and more profound, the last trace of reflex irritability is abolished, the temperature falls to 34° C. (93·2° F.), and even lower; the respiration becomes shallow, irregular and infrequent; the heart's impulse is scarcely perceptible, the countenance becomes cyanotic, and, with paralysis of the respiratory centre and of the heart, life comes to an end. Convulsions due to suffocation do not occur, since the motor centres in the medulla are also paralysed, and are no longer stimulated by the carbonised blood.

Chloral does not generally check the action of the bowels. If sufficiently diluted, it produces no injurious effects on the stomach; not infrequently it may even stimulate the appetite to a certain extent.

The pupils during the sleep produced by chloral are, as in normal sleep, contracted, and when the person awakes or is roused they dilate in the usual manner. This, however, is not the case in the sleep induced by a full dose of morphine; the myosis then continues for some hours.

During sleep under the influence of chloral the skin remains dry, unless it is acting from some other cause. The secretion of urine appears to be somewhat increased.

In childbirth chloral administered to the extent of 4 grammes (60 grains) produces no injurious effects on mother or child, whilst it mitigates the labour pains.[1]

Glycosuria is not produced in rabbits either by puncture of the floor of the fourth ventricle or by stimulating the central end of the vagus, if the animals are previously narcotised with chloral.[2]

Lastly, in favour of chloral it may be said that it can be administered for a considerable time without, as a rule, any increase of the dose being necessary, and that moderate doses can be borne for a long time without injury to the system. There are limits, however, to this. The continuous abuse of chloral hydrate leads to derangements in the system, similar to those referred to in detail as being produced by

[1] P. Müller, 'Berliner klin. Wochenschr.,' 1876, s. 356.

[2] F. Eckhard, 'Archiv f. exper. Path. u. Pharm.,' 1880, Bd. xii, s. 276.

morphine.[1] Ungar developed fatty degeneration of the heart, the liver, and the kidneys[2] in animals by administering to them for a considerable period chloral formamide, which is converted into hydrate of chloral in the intestines.

It is obvious that the indications for the use of a drug which has such a certain, clear and lasting effect on the cerebrum must be very numerous in the treatment of disease. Liebreich mentions the following conditions as probably contra-indicating its administration:—Disordered states of the *primæ viæ*, since chloral hydrate is somewhat caustic; diseases of the heart and blood-vessels, since they are both quickly affected by it; hysteria, owing to the excitement which the drug often develops in this affection; gout, because in this disease increased pain has followed the use of chloral, though why this is the case has not as yet been explained.

All sorts of so-called idiosyncrasies show themselves with the use of chloral; among which the following may be mentioned:—difficulty of breathing, resembling asthma; reddening and swelling of the conjunctiva; jaundice; and oftenest of all, cutaneous eruptions. These are of an erythematous, urticarious, or eczematous nature, but they fortunately disappear when the medicine is discontinued. A cutaneous papular eruption was particularly well marked in two cases[3] after poisonous doses; in one case 50 grammes (nearly 13 drachms) had been taken. The eruption lasted for a week. A tendency to the formation of bedsores has also been described as arising from the use of chloral.[4]

After a dose of chloral a crystallisable lævo-rotatory acid appears in the urine, named by its discoverers[5] URO-CHLORALIC ACID. It is said to have the following composition: $C_8H_{11}Cl_3O_7$. When heated with dilute sulphuric acid it

[1] Rehm, 'Archiv f. Psychiat.,' 1886, Bd. xvii, s. 36.

[2] Ungar, 'Doctordiss. von J. Willach,' Bonn, 1890.

[3] M. Litten, 'Charité Annalen,' 1877, Bd. iv, s. 194.

[4] Schüle, 'Zeitsch f. Psychiatrie,' 1871, Bd. xxviii, s. 1.

[5] v. Mering u. Musculus, 'Berichte d. d. chem. Ges., 1875, Bd. viii, s. 662; v. Mering, 'Zeitschr. f. physiol. Chemie,' 1882, Bd. vi, s. 480; E. Külz, 'Arch. f. d. ges. Physiol.,' 1882, Bd. xxviii, s. 506; E. Külz, 'Zeitschr. f. Biologie,' 1884, Bd. xx, s. 157.

splits up, through the absorption of water, into trichlorethyl alcohol, $C_2H_3Cl_3O$, and glycuronic acid, $C_6H_{10}O_7$. The salts of uro-chloralic acid and the acid itself have a soporific effect if given in sufficient doses; but sleep is induced much less rapidly and lasts longer than when chloral is taken.

The dose of hydrate of chloral sufficient to produce sleep is 0·1 to 1·0 (1·5 to 15 grains) for children, and 2 to 3 (30 to 45 grains) for adults. If considerable nervous excitement exists—as, for example, in delirium tremens—the dose must be increased. But the greatest caution must always be exercised. The German Pharmacopœia of 1890 fixes 3·0 (45 grains) as the largest single dose, and 6 (90 grains) as the maximum quantity to be given during twenty-four hours,—that is to say, the chemist is not allowed to dispense a prescription containing a larger dose than this, unless the quantity ordered by the physician is specially marked thus (!).

A case came under my notice, in all its details, of a strong man who was suffering from delirium tremens, and who died within twenty minutes after taking a single dose of 7·5 grammes (115 grains) of chloral hydrate.

It is usually prescribed in solution. If the patient is unable to swallow—as, for example, in the convulsive attacks of children—it must be given as an enema or by subcutaneous injection; the tranquillising effect following the latter method is said to be rapid and lasting. From a quarter to half a c.c. (four to eight drops) of a mixture of equal parts of hydrate of chloral and water may be used.[1] This, as may be expected, causes pain, which, however, under certain circumstances, may be considered the lesser evil of the two.

The injection of 10 c.c. (two and a half drachms) of a warm 5 per cent. solution into the empty rectum twice in quick succession has been much recommended[2] as efficacious in sleeplessness, where the remedy has to be employed for a considerable period.

The absolute purity of the chloral hydrate is a necessary condition for its therapeutic use. Blue litmus paper, dipped

[1] R. Demme, 'Bericht über das Kinderhospital zu Bern,' 1873, s. 15.

[2] Starcke, 'Berl. klin. Wochenschr.,' 1878, s. 489.

into a solution of one part in ten of alcohol, should only be tinged red on drying, and after acidifying the above solution with nitric acid, it should not, on the addition of nitrate of silver, immediately become cloudy, owing to the formation of chloride of silver. These two tests are to determine the presence or absence of an excess of hydrochloric acid.

As I apply these tests here, you see that there is a slight reddening of the litmus paper at first, whilst with the other test a slight opalescence appears in the test-tube; some hydrochloric acid may exist even in the best preparation, or it may be developed on exposure to the air, and especially to light.

When heated on the platinum-foil chloral hydrate should volatilize, and should develop no inflammable vapour. Hydrate of chloral, possessing a neutral or even an alkaline reaction from admixture with soda, has been introduced into commerce. On heating such a specimen there is a white residue which on being tested proves to be sodium chloride and soda. If any inflammable vapour is developed it arises from the presence of chloral alcohol ($C_2Cl_3OH + C_2H_6O$), the local effect of which on the stomach is stronger than that of chloral hydrate, and therefore detrimental.

Chloralum Formamidatum, chloral formamide, is a preparation which has recently become officinal. It consists of white, brilliant, odourless crystals of a slightly bitter taste, which melt at 114 to 115°, and are slowly soluble in about 20 parts of water or in 1·5 parts of alcohol. Its employment as a soporific was proposed by v. Mering in 1889.

It is prepared by mixing together anhydrous chloral and formamide ($CHO.NH_2$). It is not decomposed by the hydrochloric acid of the stomach. In the circulation, on the other hand, owing to the presence of an alkali, it absorbs water, and splits up into chloral hydrate and ammonium formiate, the latter being formed as follows:

$$CHO.NH_2 + H_2O = NH_4.COOH.$$

The formation of chloral hydrate is indicated by the appearance of uro-chloralic acid in the urine, and the formation of ammonium formiate accords with chemical

facts. It has been further assumed that sleep, which is tranquil and not too profound, is produced by the gradual separation of the chloral hydrate, and that owing to the formation of a compound of ammonium—as I shall point out to you when I come to discuss the compounds of ammonium—a gentle stimulation of the sympathetic and respiratory nervous centres simultaneously takes place. The consequence of the latter is that in animals, during the sleep thus produced, the blood-pressure and the respiration are lowered much less than when hydrate of chloral alone is employed. This property gives chloral formamide a special advantage as a soporific where disease of the vascular system exists. And it possesses a further advantage: chloral formamide is not caustic like chloral hydrate, and is therefore better tolerated by individuals with sensitive stomachs.

From 1 to 3 grammes (15 to 45 grains) produces a sleep that generally passes off without any after effects: 4 grammes (a drachm) is given in the German Pharmacopœia as the maximum dose. It may be administered either dissolved in water or as a powder.[1]

Paraldehyde was recommended as a soporific in 1883 by V. Cervello, of Palermo.[2] It is a clear colourless fluid, has a neutral or very slightly acid reaction, a peculiar ethereal but not penetrating odour, and a pungent refreshing taste; its specific gravity is 0·998, its boiling-point 123° to 125°. With 9 parts of water it forms a solution which is rendered turbid by heat. It mixes in all proportions with alcohol and ether. It is obtained by treating ordinary aldehyde, $CH_3.CHO$, at a medium temperature with a strong mineral acid; the aldehyde is thereby converted into a polymeride, that is three molecules condense into one to form $(C_2H_4O)_3$.

In warm-blooded animals paraldehyde, like morphine, acts first upon the cerebrum, then on the respiratory centre and the spinal cord. Large doses of it paralyse the respiratory centre, and as a result put a stop to respiration and the action of

[1] From the numerous papers upon chloral formamide I would select: E. Kny, 'Therap. Monatshefte,' 1889, s. 345; A. Langgaard, ibid., s. 461; v. Mering u. Zuntz, ibid., s. 565; E. Reichmann, 'Deutsche med. Wochenschr.,' 1889, No. 31 (from Riegel's Klinik).

[2] V. Cervello, 'Archiv f. experiment. Path. und Pharmak.,' 1882, Bd. xvi, s. 265.

the heart. The heart's action can be restored by artificial respiration ; it is therefore not directly affected by paraldehyde.

A dose of from 1 to 4 grammes (15 grains to a drachm) produces tranquil sleep in man without causing previous excitement or cerebral congestion. The patient usually awakes clear-headed and without disagreeable after-effects. It does not produce constipation, as is the case with morphine, nor depression of the heart's action like chloral hydrate. On the other hand, paraldehyde has the following disadvantages :—It irritates the mucous membrane of the larynx and of the stomach, if from any cause these are already affected. The system speedily becomes accustomed to it, so that the dose must be increased. Its price is rather high. The odour of the breath for at least twenty-four hours after taking the medicine is unpleasant.[1]

If the administration of large doses of paraldehyde is continued for any length of time the brain becomes affected. The symptoms approximate very closely to those produced by alcohol ; tremors, loss of memory and reason, delirium, hallucinations, and epileptiform attacks are mentioned. E. Fröhner[2] has, moreover, observed other poisonous effects on horses and dogs, viz. the formation of methæmoglobin in the blood, the degeneration and destruction of the red corpuscles, the passage of hæmatin into the urine, with diminution of the amount of these elements in the blood—results which are similar to those which pyrogallol, nitro-benzole, potassium chloride, and allied substances are known to produce. The reducing action of paraldehyde—that is, its power of readily combining with oxygen—is the cause of its injurious effect on the blood. Human blood, however, is not so sensitive in this respect as that of the animals above mentioned ; no such symptoms have as yet been observed in man, and, with ordinary caution, need hardly be feared from the usual doses.

The best form in which to administer paraldehyde is as an aqueous solution with the addition of a little syrup ; it

[1] Among other papers on the subject I would refer the reader to J. Peretti, 'Berl. klin. Wochenschr.,' 1883, No. 40 ; C. v. Noorden, 'Centralbl. f. klin. Med.,' 1884, No. 12.

[2] E. Fröhner, 'Berl. klin. Wochenschr.,' 1887, No. 37.

ought not to be given in a concentrated form, as it then causes a sensation of burning in the mouth, and also affects the stomach. The same reason renders it unsuitable for subcutaneous injection. According to the German Pharmacopœia 5 c.c. (85 drops) is the maximum single dose and 10 c.c. (170 drops) the maximum quantity to be given in twenty-four hours.

AMYLENE HYDRATE is the name of another soporific belonging to the methane series. It has the empirical formula $C_5H_{12}O$, and from its chemical behaviour appears to be dimethyl-ethyl-carbinol; that is to say, methane (CH_4) in which two atoms of H are each replaced by CH_3, one atom of H by C_2H_5, and the fourth by OH; therefore its rational formula is $(CH_3)_2.C.C_2H_5.OH$. Its characters, according to the German Pharmacopœia, are as follows:—a clear, colourless, volatile fluid with a neutral reaction, a peculiar ethereal aromatic odour and caustic taste, soluble in 8 parts of water, forming a clear mixture with alcohol, ether, chloroform, glycerine, and fatty oils, boiling at 90 to 103° C. (194° to 217·4° F.), and having a specific gravity of 0·815 to 0·826.

Its effect is purely soporific, without causing appreciable change in the respiration or circulation, and without disturbing the intestinal activity or the general condition. The medium dose for a strong adult is 2 grammes (30 grains). It cannot be substituted for morphine in the sleeplessness that is caused by pain, nor is it so easily tolerated in irritable conditions of the stomach as is the latter. On this account amylene hydrate is always given with a large amount of liquid, not less than 50 c.c. (about 4 tablespoonfuls). Extract of liquorice serves to cover its taste; it is readily taken in gelatine capsules; 4 c.c. (a drachm) is the maximum single dose. It may also be administered as an enema (5 grammes with 50 of water and 20 of mucilage). On account of its irritating properties when applied locally, it is not a suitable preparation for subcutaneous injection.

In moderate doses amylene hydrate chiefly affects the cerebrum; in larger doses it affects the spinal cord as well. Reflex excitability is lost, the respirations become less frequent and at last cease, complete paralysis of the heart meanwhile being gradually developed.

Amylene hydrate was introduced into medical practice in 1887.[1] Since that time its qualities have been much discussed, and in all essential points the original estimate of them has been confirmed.

The employment of SULPHONAL as a substitute for morphia is of more recent date: its use was suggested by A. Kast,[2] its mode of production by chemical processes having been previously discovered by E. Baumann. The German Pharmacopœia thus describes it:—colourless, odourless, and tasteless prismatic crystals, which are entirely dissipated by heat; one part of it forms neutral solutions with 500 parts of cold and 15 parts of boiling water, with 65 of cold and 2 parts of boiling alcohol, also with 135 parts of ether. It melts at 125° to 126° C.

Sulphonal, $(C_2H_5SO_2)_2.C.(CH_3)_2$, is an oxidation product resulting from the combination of ethyl mercaptan with acetone, and consequently may be regarded as methane (CH_4) in which two atoms of H are replaced by two molecules of di-ethyl-sulphonic acid, and the two other atoms of H by two molecules of methyl. The empirical formula is $C_7H_{16}S_2O_4$. It is regarded much in the same light as amylene hydrate, but as a rule sleep is not induced until several hours after its exhibition. Its lesser solubility in the intestinal canal is probably the explanation of this, which is a distinct drawback to its use. Sleep has sometimes not followed the dose for ten hours; when it did take place its character was perfectly natural. The variable effect which a given dose produces upon the same individual may be associated with this uncertainty with regard to its absorption; at one time 5 grammes (75 grains) may be ineffectual, whilst at another sound sleep may result from 0·5 gramme (7·5 grains).

Sulphonal does not produce the disagreeable after-effects which follow the administration of morphine; on the other hand, in the sleeplessness caused by pain it is powerless to produce that soothing effect on the brain which is induced by morphine. Unlike chloral, sulphonal has no irritating effect on the tissues, nor does it even in large doses affect

[1] v. Mering, 'Therapeutische Monatshefte,' 1887, s. 249.

[2] A. Kast, 'Berlin. klin. Wochenschr,' 1888, s. 309.

the circulatory system. A transitory cutaneous eruption sometimes follows its use.[1]

Sometimes after its administration, especially in women, hæmatoporphyrin, a derivative of hæmoglobin which contains no iron, appears in considerable quantities in the urine, and gives it a dark red tinge.[2] Nephritis may also follow the long-continued use of this remedy.

It is best administered as a powder, in doses for adults of 1 to 3 grammes (15 to 45 grains). The German Pharmacopœia fixes the maximum dose at 2 grammes.

Trional is the name of a new preparation which may be regarded as sulphonal modified by the substitution of a molecule of ethyl for one of the molecules of methyl in the composition of the latter. It occurs in colourless, glittering tabular crystals, which have a somewhat bitter taste. It dissolves in 320 parts of cold water, and more readily in warm water. It is easily soluble in alcohol and ether. Sleep is induced more quickly after trional than after sulphonal, and unpleasant after-effects are so rarely produced that at present it is regarded as the best hypnotic. Hæmatoporphyrin, however, appears sometimes in the urine after its administration. As an hypnotic it may be given as a powder in single doses of 1 to 2 grammes (15 to 30 grains), but like other narcotics it is injurious if taken too frequently.

Tetronal is a sulphonal which contains four molecules of ethyl, and acts in a similar fashion. It is, however, less soluble than trional, and has a more unpleasant taste. Its use, therefore, may be dispensed with.

[1] G. Merkel, 'Münch. med. Wochenschr.,' 1889, No. 26.

[2] Stokois, 'Nederl. Tydschr. von Geneesk,' 1889, ii, 413. Ranking and Tardington, 'Lancet,' 1890, ii, p. 607. Salkowsky, 'Zeitschr. f. physiol. Chemie,' 1891, Bd. xv, s. 286. Garrod, 'Journ. of Pathol. and Bacter.,' 1893, vol. i, pl. ii. In this paper it is denied that sulphonal gives rise to the presence of hæmatoporphyrin in the urine.

Cases of poisoning from morphine and chloral hydrate occur not infrequently; the former being used for the purpose of murder or suicide, or sometimes being taken accidentally: poisoning by the latter is generally the result of its being carelessly prescribed.

Morphine plays a prominent part in cases of poisoning, especially in England and America. In two years in England and Wales alone, according to Taylor,[1] 196 deaths, or nearly two thirds of all those caused by poisoning, were due to morphine. Some improvement, however, has now taken place. Still in the first half of the year 1882, in England, out of 53 deaths from accidental poisoning, 15 were caused by opium and morphine; and out of 52 fatal cases of criminal poisoning, 9 were due to the same agents, not to mention numerous cases of attempted murder in which recovery took place. Children, owing to their greater sensitiveness to morphine, supply the largest number of fatal cases. It has been computed that three fourths of all the deaths from opium were those of children under five years of age. In New York it was reckoned that within three years opium caused 60 per cent. of all the deaths which were either suicidal or due to the careless use of remedies.

The strict and very salutary laws which exist in Germany with regard to pharmacy prevent such a frightful abuse; nevertheless poisoning by morphine occurs here often enough. To take a few instances:

Twelve sleeping powders, each containing 0·01 gramme of morphine with 1 gramme of cane-sugar, were prescribed for a lady. The box was left lying about, and her son, a child of three years, got hold of it unobserved, tasted its contents, then swallowed the whole, and died a few hours afterwards.

In order to check a commencing fever in a young lady patient, a physician ordered her two powders each of which contained 0·5 gramme (7·5 grains) of hydrochlorate of quinine. It was late at night, and the apothecary's assistant being half asleep, by mistake dispensed two doses, each containing 0·5 gramme of hydrochlorate of morphine. The patient

[1] Taylor, 'On Poisons in Relation to Medical Jurisprudence and Medicine,' 3rd edit., 1875, p. 550.

took the first powder, became speedily comatose and cyanotic, and in a short time expired.

A young physician prepared a solution of 1 gramme of morphia in 20 c.c. of water, to be used for subcutaneous injections, and had it labelled "suo nomine." His syringe held about 1 c.c., and he intended to inject one tenth or one fifth only of its contents, so as to administer 0·005 or 0·01 gramme of morphine. But the first time he used the syringe he forgot, after filling it, to fix the check-screw, and on pressing down the piston injected the whole contents, 0·05 ($\frac{3}{4}$ of a grain) of morphine, under the patient's skin. He had scarcely left the house when he was hurriedly summoned back, to find his patient unconscious, with feeble respiration and small pulse. The mistake was immediately recognised, and fortunately was not followed by any injurious effect upon the patient, though it was not without detriment to the physician's reputation.

The DIAGNOSIS of morphine poisoning is easy if the *corpus delicti* happens to be discovered. Preparations of opium are recognised by their characteristic odour, if this has not been destroyed by the addition of other substances. The meconic acid reaction also, to which I have already referred, may be employed to detect the presence of opium in any solution that may be left or in any matter that has been vomited. In such a case the vomited matter should be filtered, the filtrate concentrated if necessary, and then a few drops of a solution of the perchloride of iron added. All this can be done very quickly, but the case may run too acute a course to allow time for the investigation.

Failing a trustworthy account of the preceding history of the patient, and in the absence of the *corpus delicti*, poisoning by morphine may be mistaken for that which results from large doses of alcohol, of chloral, carbonic oxide, or coal gas. Nearly all the symptoms which have been described are present in poisoning from these substances: one only is usually absent—the *strongly marked myosis*, or contraction of the pupil, which is invariably present in morphine poisoning, and which passes off only in the last stage. It is probably due to conditions in the brain, and not dependent on local action such as is produced

by physostigmine.[1] Other distinguishing marks are—in poisoning by alcohol, the distinctive smell given to the breath by the various alcoholic liquors; in poisoning by carbonic oxide, the supervention of convulsive attacks. These also occur in poisoning by coal gas, carbonic oxide being its chief noxious ingredient.

Any conditions dependent upon an increase of intracranial pressure cannot in my opinion be considered as complicating the diagnosis. The head of an individual poisoned by morphine is cool, as well as his whole body. An apoplectic seizure, or sudden congestion from any other cause, will at least raise the temperature of the head. In apoplexy, moreover, there is usually paralysis of one side of the body. In morphine poisoning the large fontanelle in young children appears to be depressed,[2] whilst in intermeningeal hæmorrhage and meningitis it bulges out.

On the strength of some complicated and rapidly performed experiments on rabbits and dogs it has been maintained, in opposition to my views, that the effect of a poisonous dose of morphine on the human heart is so trifling that it need not be taken into consideration at all.

In the first place this is negatived by experience gained on the human subject. In almost all recorded cases weak, infrequent and irregular pulsations are mentioned. Kobert[3] relates a case of this kind, in which a strong man injected himself with 0·24 gramme (3·6 grains) of morphine in a short space of time. In addition to the other symptoms of poisoning, the condition of the heart after an hour was as follows:—radial pulse scarcely perceptible, its frequency 40 to the minute, the sounds of the heart indistinct and very irregular. Artificial respiration energetically carried on produced no change. In A. Wertheimber's case above referred to (a child of fourteen days old to which 0·01 gramme of morphine had been administered), which recovered, it is stated that the heart's beat was feeble and intermittent, whilst the radial pulse was not perceptible.

In experiments on animals, with doses too small to be

[1] v. Graefe, 'Deutsche Klinik,' 1863, s. 285.

[2] A. Wertheimber, 'Archiv f. klin. Med.,' 1879, Bd. xxiv, s. 350.

[3] Kobert, 'Allg. med. Centr.-Zeitung,' 1880, s. 85.

fatal, an average lowering of the blood-pressure from 129 to 91 mm. of mercury has been noted.[1] And my assistant, H. Heubach, under the same conditions, in six experiments on dogs, noticed that the pulse sank from 120 or 130 to 42.[2] It has been further urged against my view that the diminution of the blood-pressure arose from the animal being bound down for hours, but I could easily prove that, by tying an animal down for a given period, the blood-pressure is only slightly affected, and instead of being diminished is *increased*.

In the TREATMENT of cases of poisoning our first business is to remove any poison that may be present in the stomach. In slighter cases vomiting may take place spontaneously, and may be promoted by tickling the fauces. In more severe cases morphine very soon completely suspends the excitability of the nerve-centres in the medulla oblongata, and even emetics produce no effect. It is better not to waste time with them, but at once to wash out the stomach. No other proceeding is of any use in these cases.

If strong emetics, especially the mineral ones, remain in the stomach and become gradually absorbed, they help to lessen the strength of the patient by still further lowering the activity of the already enfeebled heart. Many of the unsuccessful cases which have been recorded give the impression that the powerful emetic employed had only intensified the poisonous action of the morphine. The injection of apomorphine, which has been recommended as an emetic, and which even in small doses acts very energetically, may still cause vomiting, but it is a serious question whether the combined effect of two such extremely lowering agents does not render the patient's condition more critical than before.

In cases of poisoning by other officinal alkaloids TANNIC ACID may be administered for the purpose of rendering the poison still in the stomach less soluble, but it is of little service in morphine poisoning.

[1] C. Binz, "Ueber den arteriellen Druck bei Morphinvergiftung," 'Deutsche med. Wochenschr.,' 1879, ss. 613 und 627; und 1880, s. 149.

[2] Heubach, 'Archiv f. exper. Pathol. und Pharmak.,' 1877, Bd. viii, s. 38; A. Fick, 'Verhandl. des Congresses für inn. Med.,' Wiesbaden, 1886, s. 92.

If, for example, I pour into this aqueous solution of sulphate of strychnine a clear solution of tannic acid in water, a strong precipitate falls to the bottom, and if I mix that with some hydrochloric acid it remains undissolved. In the stomach it would consequently not be very readily absorbed. But if I now mix an equally strong solution of a morphine salt with the tannic acid no precipitate is formed. The tannic acid does not precipitate the morphine, or, more correctly speaking, the tannate of morphine that has been produced is still fairly soluble in the fluid.

If, however, tannic acid is easily procurable, half a teaspoonful in a few table-spoonfuls of water may be given, for the morphine is thereby rendered less soluble and so is absorbed less readily than before. Meanwhile the stomach-pump must be employed as soon as possible, and the stomach washed out after the usual fashion. As we now know, morphine is eliminated or excreted from the system (see page 66) into the stomach, and its re-absorption also takes place in that organ. The process of washing out must be repeated several times.

Should the natural breathing show signs of failing, immediate recourse must be had to ARTIFICIAL RESPIRATION. Faradisation of the phrenic nerve should only be attempted by one who thoroughly understands it. In a case of poisoning by chloroform—and it answers equally well in morphine poisoning—Koch placed the two poles of an induced current in the two nostrils, and allowed them to remain from ten to twenty seconds. Respiration was restored after faradisation of the phrenic nerve had been tried in vain.[1]

The following simple procedure has been recommended and successfully carried out:[2]

Pass both hands from above underneath the right and left lower ribs, draw them upwards, and then again press them downwards towards the abdomen, making both movements correspond to those of natural respiration, both in time and frequency. The individual is to be placed on his

[1] W. Koch, 'Sammlung klin. Vorträge,' 1874, Bd. iii, s. 610.

[2] M. Schüller, "Eine Modification des Silvester'schen Verfahrens der künstlichen Respiration," 'Berliner klin. Wochenschr.,' 1879, s. 319.

back, and an assistant should bend the thighs firmly upwards so as to relax the abdominal parietes.

Whilst adopting these various measures for producing artificial respiration, the maintenance of a free opening for the passage of air to the lungs must not be forgotten. Draw the tongue forward as far as possible, fix it in this position, either with the forceps, or, in default of these, by a thick thread passed through it; pass the index finger into the pharynx, feel for the epiglottis, and push it as high up as possible. The following method (Heiburg) is generally to be recommended:—An assistant stands in front of the patient, places his thumbs on the upper jaw close to the nose, and curving his fingers on both sides behind the angle of the lower jaw, pulls it vigorously forward. By pulling the jaw forward in this way the tongue and hyoid bone are also thrown forward; the epiglottis, owing to the ligaments between it and the hyoid bone being put on the stretch, is also drawn forward, and the passage to the larynx is kept free. This has been proved by experiments on dead bodies.

It has been found that artificial respiration is not sufficient to effect the re-establishment of the HEART'S ACTION when its impulse is no longer perceptible.[1] Consequently in all cases of poisoning of this character pressure must be applied to the heart in such a way that it may be alternately emptied and again filled with blood. In this way the circulation is started: the heart begins once more to contract, and the respiratory centre, which was almost completely paralysed, receives a fresh stimulus from the blood that passes to it.

In the various treatises dealing with morphine poisoning the application of all sorts of counter-irritants to the skin is recommended as an important part of the treatment, but these counter-irritants are of doubtful value when the patient's condition is so critical.

This brings me to a point in the treatment which is scarcely ever referred to in treatises on poisoning, namely, the value as a restorative, of ARTIFICIAL WARMTH CONTINUOUSLY APPLIED to the patient's body.

[1] Böhm, 'Arch. f. exper. Path. u. Pharmak.,' 1877, Bd. viii, s. 68.

A lowered temperature is one of the most constant symptoms in these cases. Both the external and internal bodily temperatures are considerably reduced. This decline is due to the incomplete oxidation of the venous blood, to the excessive loss of heat owing to the relaxed state of the cutaneous vessels, and to the relaxed condition of all the striated muscles.

An inquiry has been made into the matter.[1] The investigation did not refer to poisoning by morphine, but by chloral. The point, however, which concerns us here is an effect common to both poisons. It was clearly shown in six sets of experiments, simultaneously carried out in pairs, that a warm-blooded animal wrapped in wadding could completely recover from a dose of chloral that proved fatal to an animal of the same weight in a room of the ordinary temperature, 20° C. (68° F.); that when a dose insufficient to prove fatal was administered, recovery took place under this treatment much more quickly than without it, and that placing the animal in a room heated to 30° C. (86° F.) accelerated its return to a normal condition.

It has been proved, as the result of experience, and experimentally, that heat acts as a powerful stimulant on the respiratory centre and on the heart. Moreover in a warm room the loss of heat from the body is lessened. The practical bearing of all this is that the room in which the narcotised patient is placed must be kept at a temperature of at least 20° C. (68° F.); he must be well wrapped in blankets; if he lies in bed, warm bottles or hot bricks should be placed near him.

Good results in a severe case of morphine poisoning are said to have followed the pouring of cold water over the head, chest, and back of the patient whilst he was in a WARM BATH, 39° C. (102·2° F.). The cold douche was applied every ten or fifteen minutes over a period of about six hours, as often as the very slow respiration became insufficient; from two to three litres of water were used each time.[2]

[1] Lauder Brunton, "Effect of Warmth in preventing Death from Chloral," 'Journ. of Anat. and Physiol.,' Cambridge, vol. viii, p. 332.

[2] v. Liebermeister, 'Handb. d. Path. und Ther. d. Fiebers,' 1875, s. 622.

The action of the central nervous system must be maintained by the internal administration of STIMULANTS.

I refer in the first place to strong hot infusions of tea and coffee. They contain two stimulants, caffeine and an aromatic substance.[1] If caffeine in MODERATE doses is subcutaneously injected into animals it produces a general and active restlessness, a more rapid and deeper respiration, increased pulsation of the heart, increased blood-pressure, and a rise of temperature. These effects were strikingly manifested on dogs suffering from poisoning of a similar nature, namely, that caused by alcohol.[2]

Should there be danger in delay we must not hesitate to employ the most powerful of all internal stimulants—ATROPINE.

If a small dose of atropine, a few milligrammes, be subcutaneously injected into a dog in which, amongst other symptoms following a large dose of morphine, there is greatly diminished blood-pressure, the pressure will be increased twofold or more within a few minutes. This is due to the greatly increased number of pulsations; the beats of the heart are trebled or quadrupled, owing to a temporary paralysis of the cardiac branches of the vagi.

These branches of the vagi are the inhibitory nerves of the heart; they serve principally to relieve the brain. If, in consequence of any stimulation, the heart drives the blood too largely and too violently into the unyielding cavity of the skull, the whole brain is thereby stimulated. But by STIMULATING the vagi a slower movement of the heart's action is produced, and one cause of the excess of blood in the brain is removed. By PARALYSING the vagi just the opposite effect is produced; a quicker movement, without defective contractions of the heart, takes place, and the arteries become filled with blood.

If the vagus is exposed and divided, and its peripheral end stimulated with an induced current of low power, the heart is immediately brought to a standstill, or at least the number of pulsations is considerably diminished. If some

[1] C. Binz, "Beiträge zur Kenntniss der Kaffeebestandteile," 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. ix, s. 31.

[2] C. Binz, ibid., ss. 35—38.

atropine has previously been administered to the animal, the effect of the current on the vagus is *nil*. The atropine has transitorily so paralysed the end of the vagus that it is unable now to conduct any stimulus to the muscular tissue of the heart.

It is clear, therefore, why atropine increases the blood-pressure, whether this is in a normal condition, or lessened by morphine. The atropine does not overpower or restrain the cause of the reduced pressure, as is the case with other remedies; it only removes a continuous drag, so to speak, on the chariot, and thus a diminished motive power suffices to pull it along.

You see here a young dog,[1] weighing about 2300 grammes, in which, during the last four hours, 0·36 gramme morphine has been subcutaneously injected. The animal is absolutely unconscious and motionless. I pass a fine needle, having a small feather at the end, between the costal cartilages into the apex of the left ventricle. By observing the movements of the feather we note 52 feeble pulsations a minute. The respirations, as observed by placing a lever, with a fragment of white paper at the end, on the abdomen, are infrequent and shallow.

I now inject under the skin of the thorax 0·01 gramme atropine in a cubic centimetre of water. Very soon we notice that the oscillations of the feather increase in frequency; three minutes after the injection we note that they have risen from 52 to 118; and if I now once more inject 0·01 gramme of atropine, the respirations of the animal increase in number and extent, and soon it is half conscious. The animal that previously was perfectly motionless tries to move about, opens its eyes, and growls. The heart, the respiration, and the sensorium have therefore been beneficially influenced by the atropine—the first in the way already described, the two latter by the directly stimulating effect of the alkaloid.

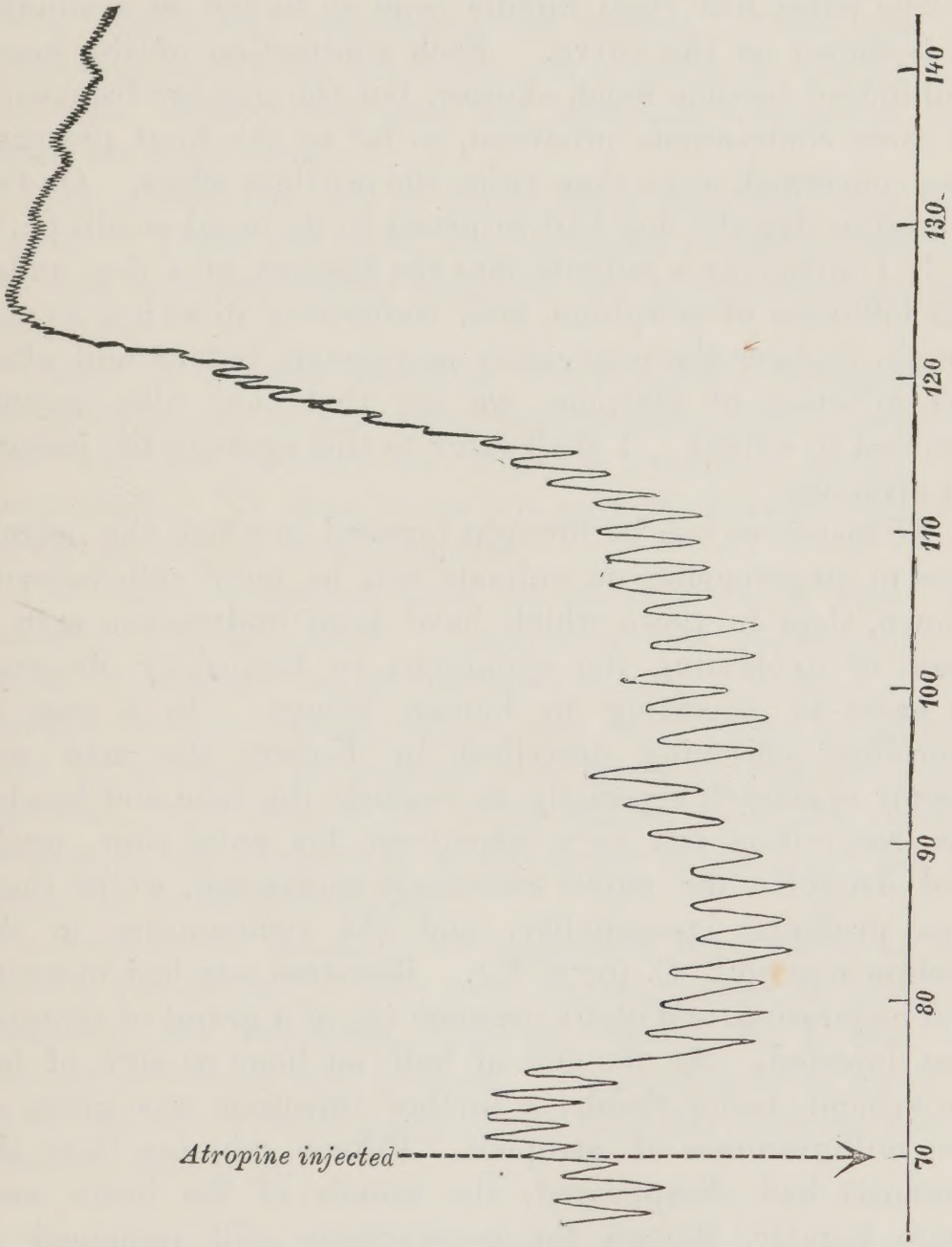
This is so simple and reliable an experiment that it invariably succeeds, if the action of the heart has been distinctly lowered by a proper dose of morphine. By employ-

[1] Compare the clinical results obtained on man by Sahli and S. Frenkel, 'Archiv f. klin. Med.,' 1890, Bd. xlvi, s. 542.

ing the hæmodynamometer it can be easily shown from the tracing on the kymograph that the increased number of pulsations corresponds to a doubled arterial pressure.

Here is such a tracing from a young dog weighing 2580 grammes.[1] Its blood-pressure was, by the injection

FIG. 2.



of 0·15 gramme of morphine, lowered to 60—80 mm., the pulse was 40 a minute, and irregular. Seventy seconds

[1] H. Heubach, "Antagonismus zwischen Morphin und Atropin," 'Archiv f. exper. Path. u. Pharm.,' 1877, Bd. viii, s. 40, Pharmakol. Inst. Bonn.

after the tracing commenced one mg. of atropine was injected. After forty seconds the pressure began to rise, and after 120 seconds the manometer indicated a pressure of 160 to 170 mm. It remained at this point for some time, and at the end of an hour still stood at from 90 to 100 millimetres of the mercurial column.

The pulse had risen rapidly from 40 to 200 in a minute, as is shown on the curve. Each contraction of the heart had indeed become much shorter, but the greater frequency of these contractions produced, so far as the total pressure was concerned, more than twice the previous effect. On the following day the dog had returned to its usual condition.

If I introduce a cannula into the trachea of a dog under the influence of morphine, and, connecting it with a kymograph, register the respiratory movements before and after the injection of atropine, we see that they also become doubled in extent. I shall refer to this again in the lecture on atropine.

No instances can be brought forward in which the usefulness of experiments on animals can be more satisfactorily shown, than in those which have been undertaken with a view of explaining the symptoms so frequently observed in cases of poisoning in human beings. In a case of morphine poisoning described by Kobert the man was deeply cyanosed, especially as regards the face and hands; his respiration was very infrequent, his pulse slow, weak, and irregular, the pupils extremely contracted, whilst there was profound insensibility, and the temperature in the rectum was 36·2° C. (97·2° F.). Recourse was had to artificial respiration, and 0·001 gramme ($\frac{1}{66}$ of a grain) of atropine was injected. At the end of half an hour no sign of improvement being visible, a further injection was given of ten milligrammes of atropine. Fifteen minutes later the cyanosis had disappeared, the sounds of the heart were more regular, though the contractions still remained at 40 per minute. In the course of the next twenty minutes ten milligrammes more were injected at different spots on the buttocks, and artificial respiration was continued. Within ten minutes more the pulse rose to 60, and the pupils regained their normal size; half an hour later the pupils

were fully dilated, the heart-sounds normal, the pulse 80, but the patient was still comatose. Afterwards the nervous system gradually recovered its sensibility to external impressions. The following morning, twelve hours after the administration of these large doses of atropine (altogether 21 times the German maximum dose !), the condition of the pulse, pupils, and respiration was normal. There was no mention of headache, but there was tingling in the fingers and toes. Some hours later the mydriasis reappeared and lasted for some days.

This is only one out of many cases recorded here and abroad.[1] There are cases, too, that give a different record, but they were improperly managed and have been obscurely described.[2]

There is nothing specially characteristic in cases of poisoning by any of the more recently introduced soporifics, such as chloral hydrate, &c., with the exception perhaps of paraldehyde. In these cases it is only the previous history which can help us to a diagnosis.

The same treatment must be adopted as in cases of poisoning by morphine. Luchsinger has shown that a heart, the action of which has been paralysed by any of the ordinary cardiac poisons, can, in the early stage, be stimulated by atropine to renewed and often to vigorous contraction. This effect is not in his opinion dependent on the removal of any obstruction to the action of the heart, but is due to its direct stimulation.[3]

Liebreich has specially recommended STRYCHNINE as an antidote for chloral. The idea was suggested to him by observing the beneficial effect of chloral in a case of rheumatic trismus and tetanus. He experimented upon a rabbit and confirmed his hypothesis that the converse would probably hold good.[4]

[1] Johnston, "Cases showing the Effects of Atropine as an Antidote to Opium," 'Med. Times and Gaz.,' 1872, p. 269; 1873, p. 175.

[2] Compare 'Archiv f. klin. Med.,' 1887, Bd. xli, s. 174.

[3] Luchsinger, 'Archiv f. exper. Path. und Pharmak.,' 1881, Bd. xiv, s. 374.

[4] O. Liebreich, 'Monatsber. d. Berl. Akad. d. Wissensch.,' 1869, s. 872.

It may be granted as theoretically possible that strychnine can act beneficially in chloral poisoning. Chloral depresses the vaso-motor centre in the brain; strychnine stimulates it:[1] the former dilates the arteries, the latter contracts them; the former lowers the blood-pressure, the latter increases it. In the narcosis induced by chloral the excitability of the respiratory centre is lowered in an extraordinary degree; in strychnine poisoning it is just as powerfully stimulated.[2] The result last mentioned can be seen in any animal previous to the appearance of the spasms; the respiration becomes more frequent and more profound.

What bearing these facts—gained from experiments on animals—may have on the point under discussion must be decided by further observations on the human subject. Whilst making such observations it should never for a moment be forgotten that powerful doses of strychnine are uncontrollable in their effects, as we shall learn more fully later on. I, for my part, should only have recourse to strychnine (0·002 gramme, *i. e.* $\frac{1}{33}$ of a grain, a few times subcutaneously) if, in a case of great danger, neither a hot bath with cold douche nor atropine was available.

[1] Sieg. Mayer, "Studien zur Physiologie des Herzens und der Gefässe," 'Sitzungsberichte d. k. k. Akad. d. Wissensch,' 1871, Bd. lxiv, s. 657.

[2] A. Christiani, 'Monatsber. d. Berl. Akad. d. Wissensch.,' Feb. 17th, 1881.

VI.

Potassium bromide—Its discovery and introduction into medicine—Experiments with it on healthy individuals—Secondary effects—Sodium bromide—Ammonium bromide—Zinc oxide—Its use in therapeutics—Poisonous action—Experiments with it—Other officinal preparations of zinc—Hemlock—Its properties—Death of Socrates from hemlock—Subsequent experience of its effects on man—Experiments on animals—Therapeutic value of hemlock—Conium hydrobromide—Hemlock sometimes mistaken for culinary herbs—Water-hemlock (Cicuta virosa)*—Curare—Its origin—Statements of Humboldt and of other travellers—Illustration of its general action on warm-blooded animals—Analysis of its effects on the frog—Curarine—Variableness of curare—Its therapeutic use.*

We now come to a group of remedies differing entirely as to their source and in their outward appearance from the cerebral sedatives which we have previously considered, but agreeing with them in some measure as to their effects. These are the bromides, of which POTASSIUM BROMIDE is the one most employed.

Its composition is KBr; it consists of colourless, cubical, shining crystals, which are not decomposed on exposure to the air. It is soluble in 2 parts of water and in 200 parts of alcohol. When a solution of it in water to which a little chlorine has been added, is agitated with ether or chloroform, either of these will on separation exhibit a red colour, which is due to the liberated bromine. Tartaric acid added to it in excess gives, after standing for some time, a white crystalline precipitate of acid tartrate of potassium; the supernatant fluid contains hydrobromic acid, the following decomposition having taken place:

$$KBr + C_4H_6O_6 = KC_4H_5O_6 + HBr.$$

A few years after the discovery of bromine in 1826 by Balard, an apothecary of Montpellier, the use of the potassium salt as a medicine came into great vogue as a remedy among French physicians. Being chemically similar to iodine, the newly discovered element had assigned to it the already well-known therapeutic properties of the former, and it was used in scrofula, syphilis, and for glandular swellings, such as goitre. On account of the corrosive effect of pure bromine, the potassium salt, corresponding to that of iodine, was prescribed, and was taken internally in quantities amounting to 30 grammes (460 grains) daily.

No improvement took place in the above-named diseases under the administration of the bromide, but its effects in these large doses on the brain were recognised. Stupefaction, giddiness, a heaviness of expression, difficulty of speech, staggering gait, diminished sensation in the extremities, abolition of reflex activity in the pharynx, were the only results of these therapeutic experiments, which, in 1850, Puche[1] in Paris termed "ivresse bromurique." Huette noticed such a complete abolition of reflex activity in the pharynx, that he suggested that the drug might possibly be of service in surgical operations.

As early as 1853, Sir C. Locock recommended bromide of potassium for epilepsy;[2] but for ten years it was rarely employed, and it was only after the lapse of another ten years, and after careful study of the records of its effects in a very large number of cases of that disease—a disease so variable, and therefore therapeutically so deceptive—that the usefulness of the remedy was unquestionably demonstrated.[3]

Since that time the physician has been in a very different position from what was previously the case with regard to the treatment of epileptic attacks, for in former times there

[1] Puche, ref. in 'Schmidt's Jahrb.,' 1850, Bd. lxvi, s. 24; Huette, 'Gaz. méd. de Paris,' 1850, p. 432.

[2] Max Donnell, 'Centralbl. f. d. med. Wiss.,' 1865, s. 46.

[3] Behrend, "On the Action of the Bromide of Potassium in inducing Sleep," 'Lancet,' 1864, vol. i, p. 607; Hitzig, "Zur Physiologie der Wirkung des Kalium bromatum," 'Berlin. klin. Wochenschr.,' 1867, s. 205.

seemed to be little or no possibility of mitigating this frightful disease. In the institution at Stephansfeld, in Alsace, thirty severe cases of epilepsy were systematically treated with large doses of bromide of potassium with the following results. In 23·3 per cent. the attacks entirely ceased during its use; in 40 per cent. the number of attacks decreased by at least one half, in the majority of these cases by more than one half; in 26·6 per cent. improvement was slight or doubtful, and only in 10 per cent. could it be said that no effect at all was produced.[1]

A further series of twenty-two cases was divided into two groups. To one half SODIUM BROMIDE only was given, to the other half only POTASSIUM CHLORIDE. After ten weeks' use of these medicines to the amount of 5 grammes (75 grains) to each patient daily, the sodium bromide had very noticeably decreased the attacks in several of the eleven patients, whilst no distinct effect was observed in the patients treated with potassium chloride.[2] Similar results were reported from the institution at Pforzheim.[3]

Bennett, of Edinburgh, reported that in 2·3 per cent. of the patients under treatment with potassium bromide the number of attacks increased; in 2·3 per cent. no change at all could be perceived; in 83 per cent. the attacks greatly decreased in number and in violence; in 12 per cent. they entirely ceased as long as the potassium bromide was taken.[4]

In addition to this, the effect which potassium bromide has in many cases of disturbed sleep is easily explicable. Senator[5] informs us that even the sleeplessness and restlessness of fever are relieved by it to a greater extent than by any other remedies. Its value has been proved also in many forms of trigeminal neuralgia. It has been

[1] C. Stark, 'Allg. Zeitschr. f. Psychiatrie,' 1874, Bd. xxxi, s. 297.

[2] E. C. Seguin records similar statistics, New York Therapeutical Soc., 1878, 8th February. In opposition to this see W. Sander, 'Centralbl. für die med. Wiss.,' 1868, s. 817.

[3] A. Otto, 'Arch. f. Psych. und Nervenkrankheiten,' 1875, Bd. v, s. 24.

[4] H. Bennett, 'Edinb. Med. Journal,' 1881, vol. xxvi, p. 706.

[5] Senator, 'Der fieberhafte Process,' Berlin, 1873, s. 207.

described as almost a specific for the vomiting of pregnancy.[1]

Clinical observation of the effects of potassium bromide had, as is so often the case, outdistanced and preceded scientific investigation, for the results of the latter remained confused and contradictory. This was due to various causes. In the experiments the effect of the POTASSIUM constituent was either not taken into account, or the results were entirely attributed to it. The experiments were made on ANIMALS which, in comparison with man, are in general much less sensitive to the action of narcotics, at least so far as the cerebral hemispheres are concerned; the experiments, moreover, were made on HEALTHY animals, without reflecting that a healthy nervous system may probably be less influenced by any sedative remedy than one which is morbidly excited; and finally, in many cases the dose employed in the experiments was far too small. A rather lengthy series of experiments from Kiel—revising all the previous investigations in the light of the increased experimental and clinical experience that had accumulated in the meantime—showed, how what had been established in the diseased, applied to the healthy, and furnished an explanation of some of the peculiarities which had been observed in the case of animals.[2]

From 10 to 15 grammes (150 to 225 grains) of potassium bromide administered to healthy young men in a single dose, or in the course of a few minutes, gave rise to oppression and a feeling of warmth in the stomach, to salivation, slight nausea, and liquid evacuations; further, to frontal headache of a dull, heavy character, as though the brain were compressed; the mental faculties were consequently arrested and the power of thought obscured. This condition lasted for several hours. Speech was slow and hesitating, words and syllables were misplaced; lassitude and insensibility to outward impressions were observed, but no sleep such as follows the ordinary narcotics. The root of the tongue, the palate, and the throat had lost their reflex

[1] N. Friedreich, 'Arch. f. klin. Med.,' 1879, Bd. xxiv, s. 245.

[2] Dr. C. Krosz, 'Archiv f. exper. Pathol. und Pharm.,' 1876, Bd. vi, s. 1.

activity; irritation of any part of the fauces did not produce the slightest tendency to vomit. The temperature was lowered from 0·5° to 1·2° C. (0·9° to 2·1° F.), and the frequency of the pulse, which was irregular, 15 to 37 per cent.; the arteries were soft and easily compressible. The effect on the temperature and pulse was most marked in the second and third hour after the dose had been taken.

Control experiments with potassium chloride showed that the effect on the heart was always largely due to the potassium. Later on we shall have yet to consider in detail the very marked effects which the salts of potassium exert upon the heart's action.

SODIUM BROMIDE, taken by the same individuals in the same manner as the potassium salt, produced the same effects on the nervous system, but not on the pulse and temperature. On animals it was also distinctly proved that the sodium salt diminishes the reflex excitability by direct action on the nervous centres. The administration of potassium bromide to dogs lessened the electric excitability of the cortical substance of the brain.[1]

Inconvenient SECONDARY EFFECTS arise from the prolonged use of potassium bromide.

Foremost among these are disturbances of the digestive function, but they can be modified or prevented by giving the medicine in a large amount of water, and not on an empty stomach.

Catarrh of the respiratory passages is developed or intensified by potassium bromide, and may assume a serious character, owing to the simultaneous abolition of the reflex activity; mucus accumulates, expectoration is impeded, and the breath becomes offensive. The mucous membrane of the eyes, nose, bladder, and urinary passages may also be affected.

In the majority of cases cutaneous eruptions appear; the most common is ACNE of the scalp, which from being punctiform may become pustular.[2] The bromide has been detected in the secretion of the pustules;[3] the production of these is

[1] P. Albertoni, reprinted from 'Lo Sperimentale,' 1881.

[2] Veiel, 'Vierteljahrschr. f. Dermatol. u. Syphilis,' 1875, Bd. i, s. 17. Kaposi has seen acne in a child at the breast, whose mother was taking potassium bromide, 'Therapeut. Monatshefte,' 1889, s. 468.

[3] Guttmann, 'Arch. f. pathol. Anat.,' 1878, Bd. lxxiv, s. 541.

due to the bromine only, for they are developed also by the two other officinal compounds, sodium bromide and ammonium bromide.[1] The acne may develop into boils. Nettle-rash, simple and nodular erythema occur; these all disappear on discontinuing the medicine.

General cachexia may be developed by an immoderate use of the bromides. The symptoms associated with it are atrophy, a sallow complexion, commencing paralysis of the extremities, loss of sexual desire, diarrhœa, trembling of the limbs, foul and coated tongue, want of appetite, mental apathy, weakness of memory, dilatation of one pupil, lateral deflection of the uvula, and even delirium and hallucinations. These symptoms are usually preceded by intense headache. There is great diversity as to individual susceptibility in the development of unpleasant effects. Recovery, as a rule, generally takes place, even from severe forms of bromism. A case of this kind has been reported[2] in which, after large doses of potassium bromide had been taken for about three years to relieve sleeplessness, marked cachexia was developed, which, however, disappeared after six months' treatment.

With regard to the ADMINISTRATION of potassium bromide in epilepsy—the disease in which its beneficial action is so urgently needed—the following method, based on the results of its use in a very large number of cases, may be recommended for adoption:[3]—a 10 per cent. solution of potassium bromide in water may be prescribed as follows: during the first week three table-spoonfuls daily, morning, noon, and evening, always about half an hour before meals; in the second week four table-spoonfuls, distributed equally over the day, but never taken immediately before or after eating; in the third week five table-spoonfuls daily, and so on from week to week, the quantity being increased by one table-spoonful up to eight table-spoonfuls daily; so that during the first week twenty-one table-spoonfuls may be given, during the second week twenty-eight, during the third thirty-five: more than

[1] Gowers, 'Lancet,' 1878, vol. i, p. 867.

[2] F. Kloepfel, 'Petersb. med. Wochenschr.,' 1880, ss. 53 und 62.

[3] A. Bertelsmann, 'Aerztl. Bericht über die rheinisch-westfäl. Anstalt für Epileptische zu Bielefeld,' 1878.

eight table-spoonfuls a day ought not to be given, and this amount must be discontinued or diminished if it seems to cause drowsiness or mental dulness. Should such a condition occur, as may be the case in isolated instances, even with seven or six spoonfuls, the quantity must be reduced. But if the attacks cease when three table-spoonfuls, for example, are taken during the day, then the dose must not be increased in subsequent weeks, but must remain at three table-spoonfuls. Only on the reappearance of an attack, or if there are warnings or indications of one impending, should the dose be increased by one table-spoonful daily, until such a quantity —it may be four, five, six, seven, or eight table-spoonfuls daily—has been reached as puts an end to their development. If for about three months there have been no attacks, the number of doses may then be as gradually diminished as they were increased. After the daily amount has been diminished to three table-spoonfuls, it will be prudent to continue this dose for two to three months longer; the quantity can then be decreased to two table-spoonfuls daily, giving this for perhaps three months, after which the medicine can be left off altogether.

If the attacks recur, the same plan of treatment must be renewed. In many cases patients cannot dispense with the potassium bromide at all, and must for years habitually take a small quantity—two, three, or four table-spoonfuls of the solution; otherwise the attacks soon return, and with even greater severity than before.

In the case of children between ten and sixteen years of age we may commence with three table-spoonfuls, but must not go beyond six table-spoonfuls at the most in the twenty-four hours. With children under ten years we may begin with two table-spoonfuls, and advance to four or five table-spoonfuls in the twenty-four hours. In the case of very young children the amount must be still further diminished.

If potassium bromide has been taken for a considerable time, or even for a few days only, by susceptible persons, it has been observed to affect the HEART unpleasantly, the pulse becoming feeble, irregular, and intermittent.

This is doubtless due to the potassium, which, constituting 33 per cent. of the salt, may very readily, given in the

large doses above mentioned, and in a form so easily absorbable, exert its depressing influence upon the heart's action. For this reason SODIUM BROMIDE is preferred by many physicians.[1]

According to the German Pharmacopœia this is NaBr, containing not more than 5 per cent. of water of crystallisation. It is a white crystalline powder, undergoing no change in dry air, but somewhat deliquescent under ordinary circumstances, soluble in one or two parts of water and in five parts of alcohol.

AMMONIUM BROMIDE, NH_4Br, is also officinal. It is a white crystalline powder, readily soluble in water, less so in alcohol, and sublimes unchanged on the application of heat. This preparation contains a larger amount of bromide than any of the other compounds—namely, 81·6 per cent. It is, however, the most easily decomposed, for by mere exposure to the air it soon becomes acid and yellowish—effects due to the formation of hydrobromic acid and bromine. There is said to be one drawback to it—namely, that it exerts an injurious influence on the digestive function. Another point to be borne in mind is the tendency, which the ammonium constituent is said to possess, to produce spasmodic contractions. As yet no precise investigations seem to have been made as to how far the presence of 18·4 per cent. of ammonium in bromide of ammonium may modify the effects of bromide in the treatment of disease.

CALCIUM BROMIDE also has been found to act as a sedative on the motor, sensory, and reflex centres in the brain and spinal cord, both in healthy and diseased conditions.[2]

The saline water of Münster-on-the-Stein, near Kreuznach, contains in 87·5 grammes of saline matter, dissolved in 10 litres of water, 0·75 gramme of sodium bromide and also of magnesium bromide. It is doubtful whether so small an amount of bromide can have any special effect when the water is used for a bath. The amount contained in the spring at Elmen, in Saxony, is larger—that is to say, of 292

[1] T. J. Hudson, 'Lancet,' 1883, vol. ii, p. 1081.

[2] Eulenburg u. Guttmann, 'Arch. f. anat. Physiol. u. wissensch. Med.,' 1873, s. 436.

grammes of saline matter contained in 10 litres of water, more than 2 grammes consist of sodium bromide.

Intentional adulterations of these salts, lessening their therapeutic value, are so improbable that we need not consider them. The tests given in the Pharmacopœia are sufficient to detect such impurities. On the other hand, the bromides may, from being imperfectly prepared, contain some bromate, or even hypobromite—that is, compounds of bromic or hypobromous acid, $KBrO_3$ or KBrO. In acid media, and consequently in the stomach, bromine would thereby be liberated—a result neither contemplated nor desirable. These impurities, as I here show you, may, if present, be detected by adding a drop of diluted sulphuric acid to some powdered bromide on a white porcelain slab, when the salt immediately becomes yellow. Hydrobromic acid, together with bromic acid or hypobromous acid, as the case may be, is liberated by the sulphuric acid. They act on each other, and bromine is set free.

In the first case we have—

$$5KBr + KBrO_3 + 6H_2SO_4 = 6KHSO_4 + 3H_2O + 3Br_2;$$

in the other—

$$KBr + KBrO + 2H_2SO_4 = 2KHSO_4 + 2H_2O + Br_2.$$

Pure bromide does not give this reaction, as the resulting hydrobromic acid, which is alone formed, is devoid of colour.

Zinc, in the form of zinc oxide, ZnO, and of zinc acetate $(C_2H_3O_2)_2 + 3H_2O$, is a substance which has been employed from a very early period for much the same purposes as potassium bromide.

Zinci Oxidum, Zincum Oxidatum, oxide of zinc, is a white, soft, amorphous powder, becoming pale yellow when heated, insoluble in water, but soluble in dilute acetic acid. It was

formerly named also *Flores zinci, Nihilum album, Lana philosophica.* For when the metal is melted in open vessels the oxidised surface takes fire, burns with a dazzling white flame, and gives off dense white fumes. This phenomenon was known long ago to Dioscorides, and compared by him to the formation of wool.[1]

Oxide of zinc was largely used formerly in the treatment of EPILEPSY and other diseases of a similar character, especially in young children, in whom opium and morphia are inadmissible. It used to be called the brain opiate of childhood. Hufeland reckoned it among the anti-epileptic specifics if given in large doses, and it continued to be used for a long period. At the present day oxide of zinc has been superseded by newer remedies, especially by potassium bromide; but even at the present time communications occasionally appear which extol the efficacy of oxide of zinc as an antispasmodic.[2] Attempts have been made to establish this theoretically from the symptoms produced by poisonous doses, and from experimental results.

Rust[3] relates that a chemist whilst preparing flowers of zinc incautiously filled the whole laboratory with the fumes, and experienced, in consequence, difficulty in breathing, vertigo, headache, sleeplessness, pain in the abdomen, vomiting, coughing, and heaviness of the limbs. The vertigo lasted until the third day, and the general weakness till the third week, when complete recovery took place.

Wibmer[4] gives an account of several exhaustive EXPERIMENTS ON HUMAN BEINGS. The first was made by Glauber in the year 1652, the others chiefly by Werneck in the year 1831. In all of them we find essentially the same symptoms as I have just described. Orfila administered oxide of zinc

[1] Dioscorides, loc. cit., Bd. i, s. 744 (*ἐρίων τολύπαις ἀμφομοιοῦται*).

[2] R. Pick, "Zwei Fälle von Spasmus Glottidis mit allgemeinen Convulsionen," 'Allgem. med. centr. Zeitung,' 1876, s. 730. v. Krafft-Ebing gave zinc acetate, as recommended by Bose, with good effect in delirium tremens to the amount of 75 grains dissolved in about six ounces of water in the twenty-four hours (see 'Encyklop. d. Med.,' 1886, Bd. v, s. 172).

[3] Rust, 'Mag. f. d. ges. Heilkunde,' 1826, s. 563.

[4] 'Die Wirkung der Arzneimittel und Gifte im gesunden tierischen Körper,' 1842, Bd. v, s. 475.

to small and feeble dogs in doses of from 9 to 18 grammes, with no further result than painless vomiting.[1]

A highly cultivated, powerful man of forty-three years of age was seized every six or eight weeks with a violent epileptic fit. The reading of a medical treatise[2] led him to try oxide of zinc in gradually increasing doses; he took altogether in five months 195 grammes (3000 grains). At the end of this time, he was pale, emaciated, and mentally dull; the tongue was heavily furred, the bowels constipated, the abdomen distended, the legs œdematous, the pulse thready and infrequent, and there was great bodily weakness. There was no vomiting throughout. During this period there had been no epileptic attacks. The medicine which had caused such disastrous results was stopped and the diet carefully regulated. In a few weeks the patient recovered, but the œdema of the feet and the constipation continued for some time longer; the epileptic attacks again returned with the same intensity as before.[3]

This case would be more instructive if oxide of zinc only had been taken, but being combined with extract of henbane and oil of chamomile, it merely shows that the amount mentioned could be taken in five months without producing PERMANENT injury. How far this may be due to the other two drugs cannot unfortunately be ascertained.

A. Michaelis specially investigated the action of zinc oxide.[4] He himself took while fasting as large a dose as 0·36 gramme (5½ grains); irritation of the stomach amounting to violent vomiting, and a general sensation of weariness, were the result. He administered within four months 72 grammes (1000 grains) of oxide of zinc to a strong dog in its food; vomiting, utter prostration, trembling of the limbs, and dulness followed, and the animal was attacked by convulsions, which recurred daily for three months; it was then killed, and gastro-enteritis was found to be present.

[1] Orfila, 'Lehrb. der Toxicologie,' ueber von Krupp, 1853, Bd. ii, s. 37.

[2] Siedler, Hufeland's 'Journal der prakt. Heilkunde,' 1831, s. 65.

[3] Busse, Casper's 'Wochenschr. f. d. ges. Heilkunde,' 1837, s. 302.

[4] A. Michaelis, 'Arch. für physiol. Heilkunde,' 1851, s. 109.

On examination the metal was found in all the organs, and especially in the brain.

The following account is from Botkin's clinic[1] at St. Petersburg. A young man had worked for twelve years in a bronze factory, exposed to the fumes of oxide of zinc; he gradually developed general cachexia, which was characterised by violent irritation of the stomach and intestines, headache, rigors, and cramp in the legs; paresis of the right side of the face and of the corresponding extremities followed. The patient stated that he had left the factory a month before he came to the hospital; the urine, nevertheless, still contained zinc. He was afterwards discharged, materially improved.

In the zinc mines of Silesia the workmen suffer from obstinate catarrh of the air-passages and of the intestines, in consequence of inhaling the fumes or the dust of zinc oxide, and this is followed by general cachexia. After having worked in the mines for ten or twelve years they often present all the symptoms of tabes dorsalis; pains in the loins, tenderness of the soles of the feet, heat and prickling in the legs, with diminished sensibility and numbness in isolated spots, increased excitability of the cutaneous and tendon reflexes, festinating and clumsy gait due to diminished muscular sensibility without atrophy or loss of electric excitability of the muscles, and finally a decrease of motor power in both upper and lower extremities.[2]

Experiments on animals have shown that inflammation, with fatty degeneration of the epithelium of the kidneys, is another effect due to the poisonous action of zinc.[3]

It is interesting, from a biological point, to find that plants can grow on soil impregnated with calamine ($ZnCO_3$), and very slowly absorb the oxide from the soil, owing to the acid secretions from the cell-walls of the roots, without their development being checked. The largest amount of oxide is found in the stems and leaves, the least in the seeds; these germinate normally, and can be eaten without injury.

[1] L. Popoff, 'Berliner klin. Wochenschr.,' 1873, s. 49.

[2] Schlockow, 'Deutsche med. Wochenschr.,' 1879, ss. 208 und 221.

[3] A. Helpup, 'Deutsche med. Wochenschr.,' 1889, No. 38. From the laboratory of Hugo Schulz.

The amount of oxide of zinc in the ashes varies from 0·5 to 1 per cent. Solutions of zinc salts so dilute even as 0·02 per cent. of the sulphate, have a very injurious effect on the growth of plants.[1]

Chloride of zinc and sulphate of zinc, the former of which is used as an escharotic and antiseptic, the latter as an astringent in affections of the mucous membranes, have also been tried internally, and produced essentially the same results as the oxide and the acetate.[2]

Zincum Aceticum, Zinci Acetas, which is sometimes administered internally as a nervous sedative instead of the oxide, consists of colourless crystalline plates, of a pearly lustre, soluble in 2 parts of water and in 36 parts of alcohol. A dilute watery solution becomes dark red on the addition of perchloride of iron. It yields with solution of potash a white precipitate entirely soluble in an excess of the reagent; this solution, if treated with dilute sulphuretted hydrogen, again yields a white precipitate.

The oxide contains 80, the acetate 30 per cent. of zinc. As, however, the latter, owing to its ready solubility, passes more rapidly into the system, its action is probably more energetic. Valerianate of zinc and lactate of zinc are, as remedies, absolutely superfluous.

Zinc oxide in the form of ointment is used as an astringent and stimulant to mucous membranes and ulcerating surfaces. These effects are probably due to the fact that it is dissolved in the acid secretions of the parts, and then, like the chloride and the sulphate, forms an albuminate. Owing to this astringent action, zinc oxide has been employed internally in intestinal catarrh. In such cases it is administered in full doses of 0·1 gramme (1½ grains) every three hours in combination with sodium bicarbonate.

It is further noteworthy that as a constituent of Lister's dressing zinc oxide has proved to be an excellent anti-

[1] M. Freytag, 'Mittheil. d. Akad. Poppelsdorf,' Bonn, 1868, Bd. i, s. 82.

[2] H. Letheby, 'Lancet,' 1850, vol. ii, p. 23; B. Testa, 'Il Morgagni,' Naples, September, 1881. A. Corradi refers to thirty-four cases of poisoning by the chloride and sulphate, 'Annali Univ. di Med.,' 1879, vol. ccxlv, pp. 197 and 306.

septic. It prevents the development of the lower organisms, lessens secretion and keeps it free from smell, and promotes cicatrisation.[1] Its beneficial local action in catarrh of the intestines is probably due to these properties.

Thus far we have been chiefly occupied with the consideration of remedies which act as cerebral sedatives. We now proceed to consider another group which act more particularly on other parts of the nervous system.

Conine is the name of an alkaloid obtained from the seeds of Conium maculatum, hemlock, a plant belonging to the Natural Order *Umbelliferæ*, and widely distributed over Germany. It is a colourless or yellowish, oily, alkaline liquid, volatilised by heat, of a peculiar penetrating odour, having a specific gravity of 0·88, and miscible in all proportions with alcohol, ether, chloroform, and oils. It is soluble in 100 parts of water, readily so in water acidulated with hydrochloric acid. Its formula is $C_8H_{16}.NH$. Geiger in 1831 was the first to obtain it in a pure form. Within the last few years it has been produced synthetically. Pyridine, C_5H_5N or $N\begin{matrix}/\!/ CH-CH \backslash\!\backslash \\ \backslash CH-CH /\end{matrix}CH$, is transformed into piperidine, $C_5H_{11}N$ or $NH\begin{matrix}\langle CH_2-CH_2 \\ CH_2-CH_2\end{matrix}\rangle CH_2$, and by the substitution of propyl, C_3H_7, in this, we obtain $C_8H_{16}.NH$ or $NH\begin{matrix}\langle CH.C_3H_7-CH_2 \\ CH_2\text{——}CH_2\end{matrix}\rangle CH_2$, propyl-piperidine, or artificial conine, which is optically inactive, but by a further process becomes optically active, and possesses all the chemical and physiological properties of natural conine.

Besides conine and ammonium salts, hemlock contains methyl-conine ($C_8H_{16}.CH_3N$) and a very little conydrine ($C_8H_{15}.OH.NH$), both of which are basic substances.

In an ancient and famous writing there is a description of the poisonous effect of hemlock on man. Plato describes in

[1] Petersen, 'D. med. Wochenschr.,' 1883, No. 25.

affecting words the death of his master by the poison cup, the contents of which were prepared virtually from the Attic κώνειον, which was noted for its strength.

"Crito made a sign to the servant who was standing by; and he went out, and having been absent for some time, returned with the jailor carrying the cup of poison. Socrates said, 'You, my good friend, who are experienced in these matters, shall give me directions how I am to proceed.' The man answered, 'You have only to walk about until your legs are heavy, and then to lie down, and the poison will act.' . . . . Quite readily and cheerfully he drank off the poison. . . . He walked about until, as he said, his legs began to fail, and then he lay on his back according to the directions, and the man who gave him the poison now and then looked at his feet and legs; and after a while he pressed his foot hard, and asked him if he could feel; and he said, no; and then his leg, and so upwards and upwards, and showed us that he was cold and stiff. And he felt them himself, and said, 'When the poison reaches the heart, that will be the end.' He was beginning to grow cold about the groin, when he uncovered his face, for he had covered himself up, and said—they were his last words—he said: 'Crito, I owe a cock to Asclepius; will you remember to pay the debt?' 'The debt shall be paid,' said Crito. 'Is there anything else?' There was no answer to this question; but in a minute or two a movement was heard, and the attendants uncovered him; his eyes were set, and Crito closed his eyes and mouth."[1]

The scene here described has been often, wholly or in part, repeated, sometimes intentionally, at other times unintentionally; sometimes for purposes of instruction,[2] or through carelessness, or by mistake,[3] and sometimes with murderous intent.[4]

A young delicate woman took four drachms of Succus

[1] Jowett's Plato, vol. ii, pp. 265–6, 1891.

[2] John Harley, 'The Old Vegetable Neurotics,' London, 1869, pp. 1 to 89.

[3] Imbert-Goubeyre, 'Recherches sur la mort de Socrate par la ciguë,' Paris, 1876, pp. 65–123.

[4] In Dessau, 1861. Reported in the 'Neuer Pitaval,' Bd. xxx, s. 98.

conii of the English Pharmacopœia, a thin fluid extract consisting of 3 parts of the fresh juice of the plant and 1 part of alcohol. Twenty minutes afterwards nausea and intoxication came on; she dropped an inkstand which she had in her hand, and was unable to walk; she was then put to bed. The symptoms increased rapidly, and in consequence of the mental agitation the pulse rose to 120; the heart very soon, however, became tranquil, but the patient was incapable of moving her arms or legs. An hour after taking the medicine muscular paralysis was almost complete; when asked to open her eyes, she found it impossible to lift her eyelids. Pulse and respirations were regular. Towards the end of another hour the symptoms subsided, and after the lapse of three hours the power to move, and the use of the limbs were quite restored. On the following day all that remained was a slight pain in the muscles of the legs.

A medical student, at a lecture where conine was handed round, took a prolonged sniff of it. About an hour afterwards, he began to feel a constantly increasing weariness, especially in the limbs, whilst he still complained of the smell in his nostrils, and of a sensation of burning in the conjunctiva; his brain was quite clear, and there was no sign of mental exhaustion. Gradually severe headache and violent throbbing in the temples came on. Two hours after the conclusion of the lecture the student, who was by that time incapable of any movement, was put to bed. His speech was affected, the whole body was hot, and there was profuse sweating; lachrymation also appeared. He could not sleep; there was a rapid flow of ideas, but he was utterly incapable of fixing any single one. By the following morning there was decided improvement. Slight exertion still readily induced perspiration, but complete recovery soon took place.[1]

These results observed in man have been investigated in detail in animals. There is a mass of literature on the subject;[2] I will now demonstrate by experiments the more important facts.

[1] Hugo Schulz, "Ein Fall von Coniinvergiftung," 'Deutsche med. Wochenschr.,' 1887, No. 23.

[2] Christison, 'Transactions Roy. Soc. Edinburgh,' 1836, vol. xiii,

I inject at one dose 0·06 gramme of conine hydrobromate in 2 c.c. of water under the skin of a rabbit weighing about 1000 grammes. For the first fifteen minutes no special effects are observed. The respiration then becomes quicker and more difficult, and is attended by general restlessness. I now inject 0·03 more; the animal can no longer hold up its head, which falls to the side, although, as you see, attempts are made to raise it. These efforts soon cease, and the head rests motionless on the table. The limbs are relaxed, the rabbit falls on its side, makes a few vain efforts to raise itself, and finally lies motionless. The diaphragm alone is still working, but the activity of this muscle soon ceases, and in thirty-five minutes after the first injection death takes place, preceded by a few short general convulsions.

Paralysis of the striated muscles commencing peripherally, and at last affecting the diaphragm, is the cause of death. The short spasmodic movements at the end are due to suffocation. That these spasms are not more marked is due to the paralysed condition of the motor nerves. The motor impulse emanating from the medulla oblongata to the periphery, and developed by the stimulation due to the presence of unaërated blood, cannot now be transmitted along the motor nerves, and consequently the violent muscular action which accompanies ordinary suffocation does not take place.

As a rule, the spasms are due to suffocation; but some animals when poisoned by conine are affected with general convulsions, although artificial respiration is being carried on at the time.[1] No explanation of this can as yet be given.

It can be shown on the frog that the muscular paralysis is peripheral, or at least that it begins in that way, and only reaches the brain after a time, or when large doses are

p. 383; Albers, 'Deutsche Klinik,' 1853, s. 370; Reuling und Salzer, ibid, 1853, s. 436; Kölliker, 'Arch. für pathol. Anat.,' 1856, Bd. x, s. 235; L. van Prag, 'Journal für Pharmakodynamik,' 1857, Bd. i, s. 1; Guttman, 'Berliner klin. Wochenschr.,' 1866, s.s. 44, 55, 76, 81; Prevost, 'Arch. de Physiol.,' 1880, s. 40; Hugo Schulz, 'Zeitschr. f. klin. Med.,' 1882, Bd. iii, s. 19; Schulz und E. Peiper, im 'Arch. f. exper. Path. und Pharm.,' 1885, Bd. xx, s. 149.

[1] J. H. Steinhäuslin, 'Doctordissertation,' unter Leitung von R. Demme, Bern, 1887, s. 61.

taken in quick succession. If we cut through a sciatic nerve and then administer the drug, this nerve is just as insensitive as the one that has remained uncut; again if we tie the crural vessels in another frog, divide the sciatic nerve, and then inject the drug, the nerve retains its sensibility. The poison must therefore come into contact with the peripheral ends in order to cause paralysis. The muscles themselves are not attacked, they react as before to a current of the same strength.

Hemlock was formerly much used in therapeutics. Dioscorides (I. 575) tells us that it is useful as a soothing ointment; that applied locally it cures herpes and erysipelas, checks nocturnal emissions, but causes wasting of the testicles and mammæ. The Hierophant, the priest who presided over the Eleusinian mysteries, and who was called upon to take a vow of chastity, rubbed his testicles with hemlock in order to render himself impotent.[1] The Abbess Hildegard (obiit 1180), who was skilled in medicine, states that a decoction of hemlock applied externally relieves the swelling caused by severe scourging.[2] Hemlock, therefore, has been included in the Pharmacopœia for centuries, and was used as a remedy in painful nervous diseases, for all kinds of tumours, in inflammation of the external parts, to check excessive secretion of milk, and for many other purposes. Its use has been gradually abandoned in Germany, owing probably to the uncertainty attendant on the action of the pharmacopœial preparations. The active agent of *Conium maculatum* is so volatile and unstable that we cannot be at all sure of its presence in either the plant itself, the extract, the plaster or the ointment.

In England the conine is better preserved by mixing the juice of hemlock with alcohol, and consequently it still continues to be employed there medicinally, and very remarkable statements as to its efficacy have been reported from that country.[3]

[1] v. Döllinger, 'Heidentum und Judentum,' 1857, s. 171.

[2] C. Binz, "Zur Geschichte der Pharmakologie in Deutschland," 'Klinisches Jahrbuch,' Berlin, 1890, s. 8.

[3] Crichton Browne, 'Lancet,' 1872, vol. i, pp. 143, 182, 217; J. Harley, "Cases of Disordered Muscular Movement illustrating the Use of

It might be supposed that any uncertainty as to its action would be obviated by using pure conine, and this has, therefore, been made officinal in some pharmacopœias; the alkaloid, however, has not succeeded in establishing itself. This may be due either to its gradual decomposition when exposed to the air, to its volatility, or its unpleasant odour, or possibly it does not really possess the special value which has been claimed for it. It was so rarely used that in 1882 it ceased to appear in the German Pharmacopœia.

Some years ago CONINE HYDROBROMATE, $C_8H_{17}N.HBr$, was introduced into therapeutics. It is a colourless salt, fairly stable when exposed to the action of the air; it consists of fine rhombic prisms, and contains 61 per cent. of conine. This preparation has all the poisonous and therapeutic properties of the pure alkaloid, together with some advantages; it is stable, does not volatilise, and when administered subcutaneously does not greatly irritate the skin like pure conine, which acts in this way very much like ammonia.

Two recent cases are instructive.[1] A boy seven years old was suffering from severe rheumatic trismus and tetanus. The experiments of H. Schulz and Peiper having shown that the spasms caused by brucine are controlled by conine, R. Demme administered this drug to him. After several subcutaneous injections of 0·0025 gramme (about $\frac{1}{30}$ of a grain) the spasms ceased, and the reflex activity was lowered. The flow of saliva was increased, respiration became more frequent, though irregular. The boy recovered. 0·0475 gramme ($\frac{7}{10}$ of a grain) of conine hydrobromate was used within five days.

A boy ten years old was suffering from traumatic trismus and tetanus following a bite of his forefinger. Treatment with conine was followed by a decided decrease in the frequency, duration, and violence of the tetanic attacks, and at last by their entire cessation for thirty-six hours. The boy died, however, from extensive pneumonia, from which he was suffering before he came to the hospital. Within forty-eight hours he had taken 0·095 gramme by the mouth

Hemlock," 'Medico-Chirurg. Transactions,' London, 1874; see also E. C. Seguin, 'Transactions Med. Soc.,' New York, Feb. 7th, 1882.

[1] R. Demme, 'Bericht über das Jenner'sche Kinderhospital in Bern,' 1886, s. 56, bis 63.

and 0·035 had been subcutaneously injected—altogether 0·130 gramme (2 grains) of conine hydrobromate.[1]

As conine hydrobromate is not officinal, samples are met with in commerce which contain a very small proportion of conine, and are therefore worthless. This has occurred in my own experience. Unfortunately this statement is applicable also to similar compounds obtained from other drugs. They are prepared in chemical works according to certain directions, but when tested are found to produce very different results from what are anticipated.

We have still to consider the way in which POISONING from hemlock may arise, by its accidental introduction into the food or drink.

The leaves and roots of *Conium maculatum* have been eaten by mistake instead of corresponding parts of *Anthriscus cerefolium* (beaked parsley or garden chervil), *Petroselinum sativum* (common parsley), *Pastinaca sativa* (parsnip), *Cochlearia armoracea* (horse-radish), and *Chærophyllum bulbosum* (bulbous chervil), which is also cultivated in some districts and used as a culinary plant.

It should be borne in mind, in all cases of poisoning by conine and its preparations, that it kills by directly paralysing the respiration, and by immediately lowering the temperature. The energetic maintenance of artificial respiration and the application of warmth to the body are, therefore, of the first importance, and should be tried as soon as possible.

With regard to the recognition of these umbelliferous plants, it must be remembered that it is sometimes difficult, if we have only parts of the plants before us, to distinguish them from one another. Very often the only way of doing so is from the odour developed from the leaves or seeds when bruised between the fingers, or still better when rubbed in a mortar with a few drops of lime water.

Another species of hemlock, water-hemlock or cowbane, CICUTA VIROSA, is only noteworthy as being a deadly poison.[2]

[1] See also the report of the Bernese hospital to which reference has just been made, pp. 28 to 42.

[2] R. Böhm, 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. v, s. 279.

CURARE, the South American arrow poison, is a dry extract somewhat like opium in appearance, of a dark brown colour and a bitter taste. The Indians of the South American tropics prepare it—as A. von Humboldt and others[1] have described at length—chiefly from the bark and sap-wood of *Strychnos toxifera, cogens,* and *Schomburgkii.* They add also portions of a considerable number of other plants, believing, quite without reason, that these also are essential to the excellence of the preparation. Arrows poisoned with curare were first brought to Europe in 1595 by the English admiral Walter Raleigh.

The Indians on the Orinoco, on the Amazon, and in Guiana dip the points of their arrows in the fresh extract, and so use them in battle or in hunting game. "I know the white men understand the art of making soap and the black powder, but the misfortune is that it makes a noise and frightens the animals if the shot misses them. With us the art of making curare is transmitted from father to son, and it is better than anything that you can make over there. It is the juice of a plant that kills quietly, and nobody knows where the shot comes from." Such are the laudatory terms in which the Indian spoke of his preparation. When fresh its effect is very powerful. "Large birds hit in the thigh by one of these poisoned arrows die in from two to three minutes, wild boars in from ten to twelve minutes. A carpenter (of Humboldt's company), a man of uncommon muscular strength, incautiously rubbed the curare on an arrow between his fingers, where he had a trifling wound. He fell to the ground seized with vertigo, which continued for half an hour. Fortunately the curare was a mild kind used for killing very small game. . . . A man wounded with these arrows feels fulness about the head and giddiness, so that he is unable to stand; then follow nausea, repeated vomiting, burning thirst, and a feeling of numbness about the wounded spot."

Humboldt was aware of the fact that curare "becomes weaker by transmission through damp countries." This is

[1] A. v. Humboldt, 'Reise in die Aequinoctial Gegenden Amerikas,' 1799 bis 1804, 1860, Bd. iv, s. 80; Appun, 'Unter den Tropen,' Jena, 1870

still the case with the curare of commerce; but it is only its virulence which is diminished, the character of the poison remains the same.

I inject into a grey rabbit weighing about 2000 grammes one c.c. of water containing 0·015 gramme of curare. The heart beats at the rate of 150, whilst the respirations number about 120 in the minute. The pupils are of medium size.

In four minutes there is excessive secretion from the lachrymal glands. In six minutes the head falls forward; the animal makes fruitless efforts to raise it. In seven minutes the animal is lying on its side; respiration is less frequent, but still active: the pupils are unaltered. In nine minutes respiration is infrequent and very shallow; the eyeballs protrude, the pupils are contracted. In ten minutes several very short respirations and quiverings can be seen: the heart-beats are still vigorous and above eighty a minute. In twelve minutes the pupils are dilated, and there is no respiratory movement. In fifteen minutes, on exposing the heart it is seen to be still beating vigorously at the rate of seventy a minute. The blood is dark, but becomes bright if it is agitated with air.

What is the cause of this rapid and general paralysis? Are the nerve-centres, the motor nerves, or the muscles the parts affected?

The problem is solved by an experiment on the frog,[1] which shows that THE TERMINAL ORGANS OF THE MOTOR NERVES are the parts first affected by the curare.

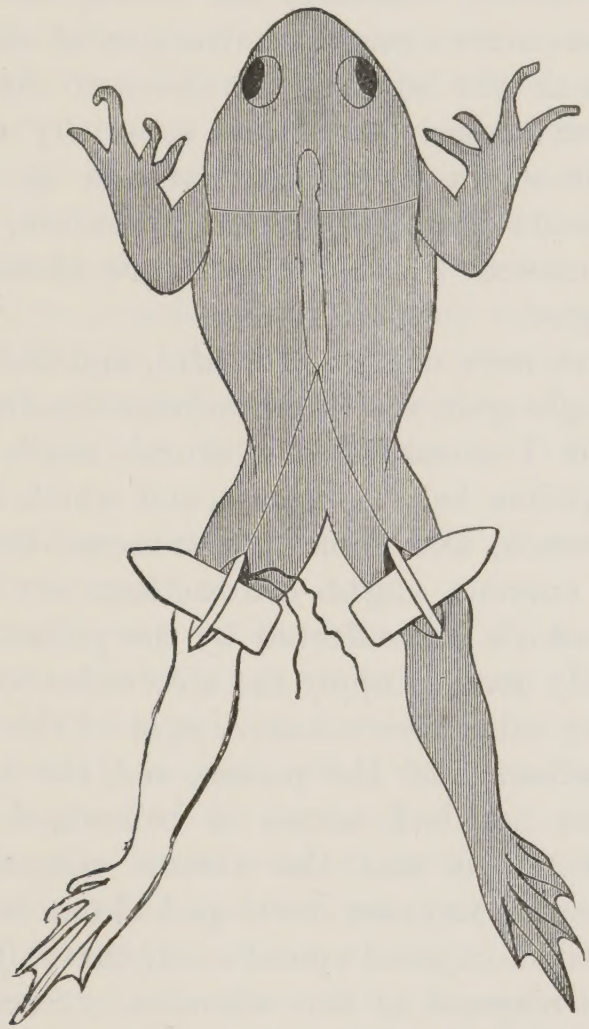
In this active and vigorous frog I have exposed the sciatic nerve in the upper part of the thigh, and have tied the femoral artery in one leg close to the knee-joint. I now inject subcutaneously into the back 0·0001 gramme curare in 0·5 c.c. of water; the frog's head soon begins to droop, and if the bell-glass is removed, it no longer attempts to spring; respiration has ceased, the animal is paralysed.

The two femoral nerves having been thoroughly insulated by means of small glass slides placed underneath them, I

[1] Cl. Bernard, 'Leçons sur les effets des substances toxiques et médicamenteuses,' 1857, pp. 305 et 461. This analysis of its action in the year 1850 was followed by a series of papers by other investigators.

stimulate them, one immediately after the other, with a very feeble induction current; only the muscles of the leg and toes of the side on which the artery was tied contract; there is no movement whatever on the side in

FIG. 3.[1]



which the artery is free. Where the poison did not reach the periphery the part is unaffected. The commencement, therefore, of the paralysis is peripheral.

I now expose the muscles of the legs and apply the electrodes to corresponding parts on the two sides. In every instance contractions of equal rapidity and strength are produced. The irritability, therefore, of the muscles remains

[1] In the accompanying figure, the meaning of which is explained in the text, the SHADED portion indicates the portion affected by the MOTOR PARALYSIS induced by the curare.

unaltered, even where a stronger stimulation of the nerve, obtained by approximating the two coils of the battery, no longer produces any contraction. The paralysis affects solely the motor endings of the nerves.

If I expose the femoral nerve in the pelvis, and as before tie the artery of the same side at the knee, and then, after injecting the curare, stimulate the nerve, we see that the stimulus of the current causes contraction of the muscles of the lower part of the leg, but not those of the upper part. This particular experiment more especially demonstrates that the TRUNK of the nerve has not lost its conductivity in addition to its irritability; that, therefore, the parts of the nerve enclosed in the muscle are those which are primarily affected.

If the curare were not too powerful, and did not act too rapidly, we might gain still more information from the same animal; for if I stimulate the crural nerve of the leg to which the poison has had access, and which is completely under its influence, and somewhat increase the strength of the galvanic current, slight contractions are observed in the other leg which is unaffected by the poison. But more than this, I only need to apply the electrodes to, or nip with the forceps any otherwise sensitive spot of the body which is under the influence of the poison, and the leg to which the poison has not had access is convulsed. The only explanation of this is that the REFLEX GANGLIA not being paralysed, a motor impulse developed there is transmitted through the still uninjured spinal cord, the only part which is still able to respond to the stimulus. Sensation, reflex excitability, and conductivity of the spinal cord, therefore, still exist, though the motorial end-plates of the nerves are paralysed.

Opinions differ as to whether the SENSORY NERVES are also paralysed by curare. According to the most recent investigations [1] they are not.

There is a still simpler method of proving that the NERVE-ENDINGS in the muscles are directly affected by curare. I have here a weak solution of curare in water containing 0·7

[1] J. Tillie, 'Arch. f. exper. Path. u. Pharmak.,' 1890, Bd. xxvii, S. 1.

per cent. of sodium chloride (distilled water acts injuriously on recently exposed tissue ; but 0·7 per cent. of NaCl obviates this). Two preparations of muscle with the nerve attached have for some time been kept in this solution, in the one case only the nerve being immersed, in the other, only the muscle. On testing them electrically the following result is obtained : both muscles respond equally well when the electrodes are brought directly in contact with them, whilst the nerves respond very differently. On stimulating the nerve of the first preparation the muscle contracts ; stimulation of the nerve of the other produces no result. In it the terminals of the nerves are saturated with and paralysed by the curare absorbed by the muscle from the solution, and, consequently, no impulse is transmitted through them when the nerve-trunk is irritated. The stimulus meets with some extraneous resistance in the nerve-endings within the muscle, and therefore does not pass on to the muscular tissue itself.

We have still to consider the effect of curare upon the other important organs of the body.

It is not very easy in experiments on animals to accurately determine the effect upon THE BRAIN. From what has been observed in animals and in man we may conclude that curare has only a slight effect upon the brain, and that the same holds good of the entire medulla.

As regards the HEART and VASCULAR SYSTEM, what was partially demonstrated in the previous experiment holds good, but if stronger doses continue to act for some time, the pulse then becomes very frequent and weak, and the blood-pressure falls. The effect on the circulation is caused by paralysis of the vagus and consequently of the heart; the fall in the blood-pressure arises from simultaneous paralysis of the vaso-motor nerves, which causes a general dilatation of the systemic arteries.

We have already seen in the rabbit that one of the first symptoms to appear was excessive secretion of the lachrymal glands. This, as well as a similar increase in the secretion of the saliva and of the urine in animals, has often been described and explained as being due to stimulation of the SECRETORY NERVES.

Sugar appears in the urine of animals poisoned by curare, both when they are fasting and the liver therefore is free from glycogen, and also after they have been fed. The sugar is probably due to the asphyxia.

Statements have differed widely as to the effect of curare on the TEMPERATURE. It is now proved that in an animal poisoned by curare, and kept alive by artificial respiration, the TEMPERATURE falls considerably, and simultaneously the consumption of oxygen and the formation of carbonic acid are diminished. This is said to arise from the relaxed condition of the large muscles of the body, and the consequent diminution of the metabolic processes.[1] The process of oxidation in the muscles is for the most part dependent upon their uninterrupted innervation, and therefore must cease under the action of curare. The regulation also of the temperature, which probably depends primarily on a continuous slight reflex stimulation of the motor nerves, varying according to the difference of temperature between the animal and its environment, is also reduced to a minimum under the influence of curare.

If such quantities of curare, as are, when subcutaneously injected, distinctly and rapidly poisonous, be given by the mouth to animals soon after food, very frequently poisonous effects are not produced. This has long been known, and was at first attributed to some destructive property of the gastric juice upon the poison. Claude Bernard, who showed that curare was not acted upon by the gastric juice, attributed the immunity to deficient absorption. The slight and uncertain effect which it produces when taken into the stomach, is, however, due to the fact that its elimination by the kidneys is very rapid in comparison with its absorption by the stomach, when this contains food. If the stomach is quite empty, or if the ureters are tied before administering the poison, its full effect is produced.

Sufficient curare passes into the urine to make it poisonous. Bidder took some urine from the bladder of a frog three days after the curare had been given to it, and injected this

[1] Zuntz und Röhrig, 'Arch. f. d. ges. Physiol.,' 1871, Bd. iv, s. 83; Riegel, 'Centralbl. f. d. med. Wissensch.,' 1871. s. 401; Zuntz, ibid, 1882, s. 561; und 'Arch. f. d. ges. Physiol.,' 1891, Bd. xlix, s. 423.

subcutaneously under the back of a second frog. In twenty-five minutes it was completely paralysed. Two days afterwards a third frog was similarly treated with the urine of the second ; in thirty minutes it was motionless. Then the urine of the third frog was transferred to a fourth ; the result was the same as before. The contents of the gall-bladder and lymph sac were harmless.

Here we have the contents of the bladder of the rabbit which we previously killed with curare. I add to it one drop of sulphuric acid, and then a few drops of a concentrated solution of iodine and iodide of potassium. A beautiful brown precipitate is produced, which shows the presence of an alkaloid.

All attempts to produce curare in a crystalline form have been hitherto unsuccessful. We only know that its activity is due to an alkaloid, the formula for which, from its combination with platinum, has been calculated[1] as $C_{18}H_{35}N$. A crystalline body is obtained on decomposing CURARINE by heating it with acids, but this is inactive. Pure curarine is extremely poisonous. For a rabbit weighing one kilogramme the fatal dose is 0·00035 gramme ; for a medium-sized frog 0·00004 gramme. In the case of the rabbit death takes place in from ten to fifteen minutes.[2]

According to Böhm there exists in some specimens of curare a second alkaloid, which he has isolated and called curine ; it is, he says, much less poisonous than curarine, but in experiments, especially on warm-blooded animals, its presence may modify the results, as it directly paralyses the heart's action.

In using curare for any purpose we have solely to depend upon the old extract prepared by savages, and this is a great obstacle to the introduction of the remedy into medical practice. Its composition is very uncertain and variable, and we do not possess the slightest security against intentional adulterations of it ; whilst, when exposed to damp air, it rapidly deteriorates and becomes inactive. In

[1] Th. Sachs, 'Annalen der Chemie,' 1878, Bd. cxci, s. 254 ; W. Preyer, 'Allgem. Wiener med. Ztg.,' 1879, s. 554.

[2] R. Böhm, "Chemische Studien über das Curare," from the 'Beiträge zur Physiologie,' 1887, s. 173.

aqueous solutions this change seems to take place still more quickly.

We have here a 0·1 per cent. solution of this nature, which I made several months ago with boiling distilled water; I filtered the solution carefully, and poured it into the bottle, but now there appears to be a mucus-like substance mixed with it. I have under the microscope a preparation of this substance. It consists of a thick deposit of fungus-like filaments, the upper half of which contains a mass of yellowish-grey spores in the form of a spike. It is evident that so large a formation of fungus in a preparation of this kind cannot take place without some essential change in the substances in the solution. We see, therefore, how such solutions may become inert.

It was natural that a remedy which has such a powerful action upon the motor nerves should be tried in diseases in which convulsions occur. It was experimented with, chiefly in France and Italy, in tetanus, hydrophobia, and epilepsy. Busch was the first, in 1866, among German physicians to treat patients with curare who had been wounded and were suffering from tetanus. I myself witnessed the good effects following its use when in charge of a division of the field hospital at Nechanitz, near Königgrätz. The spasms subsided in most cases after the first injection, but they returned in all their former strength as soon as the effect of the curare had passed off. This method of treatment was much liked by the patients, and they would beg for a repetition of the dose with the greatest anxiety as soon as they felt that the spasms were about to return. Busch[1] afterwards used curare for cases of this sort in his clinic, and for the most part with beneficial results. A real cure is not to be expected from the use of this drug, nor would such a result correspond with the nature of tetanus. Curare has no effect upon the cause of this disease, but merely alleviates one of its symptoms. Even local outbreaks of tetanus—I had the three cases at my station in one room, whilst Busch had eight in the riding-school, of Hradek Castle—seem to indicate that a poison of the

[1] W. Busch, 'Niederrhein Ges. f. Natur- u. Heilkunde,' Bonn, 1867, 17 Mai.

same character in all these cases, the effect of which is not weakened by curare, is generated in and absorbed from the wound, and that too for a considerable time.[1] Curare acts in these and other irritable conditions of the reflex centres, as morphine and chloral do in the continuous insomnia which occurs in certain cases of typhoid fever. In those cases of tetanus in which death occurs in a few days, through exhaustion of the nervous centres, the transient depression of the motor nerves may alleviate the symptoms: less acute cases tend of themselves towards recovery.

The subcutaneous injection of curare has proved useful in alleviating the symptoms in several cases of hydrophobia in man,[2] and once in a case of hysterical hydrophobia.[3] In one of these cases nineteen doses, containing altogether 0·38 gramme ($5\frac{3}{4}$ grains) of curare, were injected in the course of twenty-two hours, with the following result:—"The patient breathed quietly and became indifferent to draughts of air the strength of which was purposely increased." Previously there had been constant excitement, convulsions on swallowing, extreme dread of water and of draughts of air. "In the course of the forenoon he repeatedly asked for brandy on account of his great thirst, and twice took some; further in the afternoon he succeeded without any difficulty, whilst standing, in drinking a cup of coffee." An unfortunate occurrence rendered the continuation of the treatment apparently impossible, and the patient died in a condition of wild excitement.

In the literature on the subject many cases are recorded of experiments on animals, from which it has been concluded that spasms which originate in the nervous centres cannot be arrested by curare. It should have been obvious, for the reasons above given, that these spasms can be controlled by curare, for it is impossible to understand how any im-

[1] This has since been proved by the excellent work of L. Brieger in Berlin.

[2] F. A. Hoffmann, Berliner klin. Wochenschr., 1879, s. 637; v. Hake, 'Deutsche med. Wochenschr.,' 1880, s. 535; Pentzoldt, 'Berl. klin. Wochenschr.,' 1882, s. 33.

[3] Offenberg, 'Geheilte Hundswut,' Bonn, 1879.

pulse from the nervous centres is to reach the muscles if curare, by acting on the terminal organs, puts an obstacle there to the further transmission of the impulse. Certain experiments which I myself began, and which one of my pupils continued and published,[1] have proved that curare is able even in animals to arrest the spasms originating in this way. These experiments have meanwhile been superseded by the results which have been obtained in the human subject.

We have still to consider THE TREATMENT of persons who have been poisoned by curare. Moderate doses kill simply by paralysing the respiratory movements. We can consequently avert this danger by establishing artificial respiration. Sir B. Brodie long ago gave a practical demonstration of this.[2] He put some curare into a wound of a small tom-cat. The animal was paralysed; respiration ceased, but the heart still continued to beat 104 times a minute. Brodie now placed the animal in a temperature of about 30° C., and pumped air into its lungs. The heart continued to beat regularly, the iris was contracted, saliva and tears were secreted, but the animal still remained motionless. Artificial respiration was continued, and at the end of an hour there were a few shallow respiratory movements; at the end of another hour spontaneous respiration was established. The animal now slept soundly for forty minutes, then got on its legs and walked about. A patient who has been treated with curare ought always to be watched, and everything must be in readiness for tracheotomy, although, as far as I know, this has never yet been necessary.

Large doses of curare, and sometimes small doses if continued for a long time, paralyse not only the motor nerves, but the heart also, and perhaps other organs. Artificial respiration goes a very short way towards counteracting this. Every means of stimulation must be used, but whether the result will be successful or not is doubtful.

[1] Th. Braun, 'Das Americanische Pfeilgift Curare als Heilmittel,' Doctordissert., Bonn, 1880.

[2] B. Brodie, "Experiments on the Action of Poisons," 'Phil. Trans.,' 1812, vol. xl, pp. 279, 410; and 1811, vol. xxxviii, p. 173.

From the earliest times a shrub has been cultivated in Peru, the leaves of which the natives value highly as an indispensable luxury, just as other nations value alcohol or tobacco. Lamarck, in 1749, named the plant ERYTHROXYLON COCA; Niemann, a pupil of Wöhler's, isolated an alkaloid from it in 1860, which he named cocaine; and this alkaloid has recently been added to the list of remedies.

The officinal form is COCAINUM HYDROCHLORICUM, Cocainæ Hydrochloras, hydrochlorate of cocaine. It consists of colourless, translucent, odourless, anhydrous crystals, yielding neutral solutions with water and with alcohol. The crystals have a bitter taste and cause a temporary numbness of the tip of the tongue. The salt has the empiricial formula $C_{17}H_{21}NO_4.HCl$. By heating cocaine with acids or with caustic baryta in a closed test-tube it is decomposed, with absorption of 2 mol. of water, into methyl alcohol, benzoic acid, and a basic substance, ecgonine ($C_9H_{15}NO_3$):

$$C_{17}H_{21}NO_4 + 2H_2O = CH_3.HO + C_6H_5.COOH + C_9H_{15}NO_3.$$

Besides cocaine the leaves contain benzoyl-ecgonine, and another base, hygrine, neither of which possesses any medical importance.

Cocaine illustrates in a remarkable way the slow progress which is made in our knowledge of the therapeutic value of familiar substances. Thirty-five years ago Wöhler reported upon its very striking and interesting property in the following terms:[1]—"It has a bitter taste, and has the peculiar effect upon the nerves of the tongue of making the point of contact temporarily numb, and almost devoid of sensation." This is a clear statement of a fact which in our days excited the keenest interest. In 1879 B. von Anrep[2] discovered that when this alkaloid is injected subcutaneously, the skin becomes insensible to the prick of a needle in the neighbourhood of the spot where the injection has been made, and that it has the same effect if it is painted over the tongue; and he therefore recommended it as a "local

[1] Wöhler, 'Annal. d. Chemie u. Pharm.,' 1860, vol. cxiv, s. 216.

[2] B. v. Anrep, 'Arch. f. d. ges. Physiol.,' 1879, Bd. xxi, s. 38. In Rossbach's Laboratory at Würzburg.

anæsthetic," but it was not till the year 1884 that a physician made use of this discovery in practice.[1] Since that time numerous experiments have been made with it on animals, and it has been employed on man with good results.

I apply an induction current to the eyeball of this large rabbit; the animal at once turns its head aside, and would fall off the table unless prevented. I now pour a few drops of a 10 per cent. solution of cocaine hydrochlorate into its eye and hold the lids down for half a minute. I wait another minute, and on applying to the eye the same current, you notice that the animal offers less resistance than before. Three minutes later the eye becomes insensible to the current even if I increase its strength so much that, on looking closely, you can see sparks passing between the electrodes and the cornea. The eye into which I put no cocaine, on the other hand, reacts as the other did at first. Only the sensory nerves are affected by cocaine, for if I now apply the current to the eyelids, we notice that they immediately contract and close. The experiment demonstrates that there is no effect produced upon the central nervous system such as occurs with morphine, and that this is the case can easily be proved by a similar experiment on the human eye; the cornea becomes insensible without there being any loss of activity in the brain. As regards the human eye, a slight sensation of burning, followed by one of dryness and cold, is felt at first after the application of the drug. The cornea is pale and dry; the pupils are dilated, but still react to light; accommodation is only slightly impaired; the intra-ocular pressure, after a slight transitory increase, is diminished. The insensibility lasts about half an hour, though the dilatation of the pupil may last for a day. This is all due to paralysis of the nerve-endings of the trigeminus, and stimulation of those of the sympathetic. The mydriasis appears to depend upon the latter, as vascular constriction and bloodlessness of the vessels simply contract the iris.

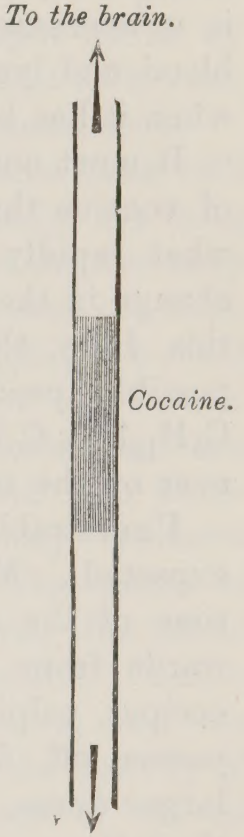
This local constriction of the vessels also takes place

[1] K. Koller, "Ueber die Verwendung des Cocains zur Anästhesirung am Auge," 'Wiener med. Wochenschr.,' 1884, s. 1276.

in mucous membranes which have been painted with solution of cocaine. Narrow passages—for example, the inside of the nose—are thus rendered more accessible to examination, apart from their diminished sensibility.

The sensory nerves are paralysed in their course as well as at their terminations. A large rabbit, lying on its belly, is fastened to this frame; about 4 cm. (1½ inches) of its sciatic nerve are exposed and a strip of cardboard is placed underneath this. I now come to the experiment which is depicted here: at "cocaine" I apply all round the nerve finely powdered cocaine with a drop of water, and then wait a few minutes. If I now stimulate the nerve at the part "to the brain" with a very weak induction current, the animal becomes extremely restless from pain, and the leg is tetanized from above downwards. If I stimulate the part at "cocaine," the animal remains quiet even when the current is greatly increased, but the foot is tetanized as before. The cocaine therefore has had an inhibitory action upon the substance of the sensory nerve-fibres, but has for the present left the motor fibres unaffected. If, however, we wait a little longer, we shall see that no motor impulse can pass "cocaine." Finally, if I stimulate the portion towards the periphery, the foot becomes violently tetanized, though there is no indication of pain.

Fig. 4.



This rapid paralysis, first of the sensory and then of the motor nerve-fibres, which quickly passes off after the removal of the cocaine, is a property peculiar to cocaine alone among all the alkaloids with which we are acquainted. The others have precisely the same effect as common salt, stimulating the nerve in both directions in consequence of the withdrawal of moisture from the tissue.[1]

[1] The conditions mentioned were in 1886 observed and described independently by four observers: H. Alms, 'Arch. f. Anat. u. Physiol.' Physiol. Abtheil., Suppl., s. 293; J. Feinberg, 'Berl. klin. Wochenschr.,'

I need not further explain how frequently the properties of cocaine which I have shown you are useful medicinally. The experience of the last five years teaches us that peripheral pains in the body are removed, or at least mitigated, by its action, and in a manner not previously attainable. Generally from 0·01 to 0·03 gramme ($\frac{1}{7}$ to $\frac{1}{2}$ grain) is sufficient, either dropped in solution or painted upon the part affected, or injected under the skin or tissue.[1] In the last two cases it is necessary to prevent as far as possible any oozing of blood and lymph, because cocaine only acts with certainty when it has been in contact with the tissues for a short time.

It must not be forgotten in applying ready-made solutions of cocaine that in this form the activity of the drug somewhat rapidly diminishes, apparently from some molecular change in the cocaine, although we may be unable to detect this from the appearance of the solution. One of the possible products of decomposition is benzoylecgonine, $C_9H_{14}NO_3.C_7H_5O$, which is said to produce no effect whatever on the sensory nerves.[2]

Undesirable SECONDARY EFFECTS from cocaine must be expected. Most persons who have an injection for the first time of the above-mentioned amount suffer shortly afterwards from slight headache, a peculiar sensation in the occiput, palpitations, and vertigo. Usually all this quickly passes off, but in other cases, and almost always after larger doses, nausea, pallor, and severe fainting fits occur; the latter may terminate with convulsions, which resemble those of chorea or epilepsy. Mental disturbance, sometimes amounting to hallucinations or to maniacal excitement, has been frequently observed.[3] These secondary effects are naturally very various, according to the personal idiosyncrasies of those who take the cocaine, and also according to

s. 52; W. Koch's 'Centralbl. f. klin. Med.,' ss. 793 u. 889; A. Witzel, 'Deutsche Zahnheilkunde,' Heft 1, s. 5. The arrangement of the above experiments differed, but not in any essential particular.

[1] L. Pernice, 'Deutsche med. Wochenschr.,' 1890, No. 14.

[2] Ralph Stockmann, 'Proc. Roy. Soc. Edin.,' 1887, p. 771.

[3] See the tabulation of 174 cases by E. Fulk, 'Therap. Monatshefte,' 1890, ss. 511 u. 642; also F. Mannheim, 'Zeitschr. f. klin. Med.,' 1890, Bd. xviii, s. 380.

the dose and method employed in giving the drug. As the brain is rendered anæmic by cocaine, the head of a person who has had an overdose ought to be placed low, and from three to five drops of nitrate of amyl should be inhaled, as this effectively expands the vessels of the brain.[1]

When cocaine is applied directly to the surface of the eye, care should be taken to prevent evaporation, otherwise loss of the epithelium of the cornea very soon takes place.[2] This loss is due to excessive evaporation brought about by defective closure of the eyelid, and by diminished lachrymal secretion, one of the results of the vascular constriction.

The so-called PHYSIOLOGICAL EFFECTS of cocaine have still to be discussed. In man, when taken internally, the drug produces a diminished feeling of hunger and of the necessity for food, with an increased capacity for physical exertion. On account of these properties the plant is highly esteemed by the South American Indians, who chew the leaves. Diminished secretion of urea and of phosphoric acid has been noticed in animals ;[3] whilst the sugar was also somewhat diminished if they had been previously rendered diabetic by being fed with phlorizine. The action of cocaine on the nervous system of animals proves that taken in moderate doses it is at first a powerful stimulant.[4] Under its influence thermogenesis,[5] the blood-pressure, and the number of respirations are increased ; and if the activity of the two latter has been diminished by means of chloral hydrate, or any drug with a similar paralysing action, cocaine will restore it. Large doses cause death, primarily by stimulating the respiratory centre, thereby inducing tetanus of the respiratory muscles, and secondarily by the paralysis of the nerve-centre which follows this stimulation.

[1] Schilling, 'Münch. med. Wochenschr.,' 1893, No. 40.

[2] O. Eversbuch, 'Münchener ärztl. Intelligenzblatt,' 1885 (published separately) ; L. Würdinger, 'Münch. med. Wochenschr.,' 1886, s. 131, *et seq.*

[3] R. Fleischer, 'Arch. f. klin. Med.,' 1888, Bd. lxii, s. 82.

[4] Tumas, 'Arch. f. exper. Path. u. Pharmak.,' 1886, Bd. xxii, s. 107, und 'Arch. f. d. ges. Physiol.,' 1890, Bd. lvii, s. 553; U. Mosso, ibid., 1888, Bd. xxiii, s. 153.

[5] E. J. Reichert, 'University Med. Magazine,' May, 1889.

Very small quantities of cocaine—commencing with doses of one mg. and increasing them to three mg. (from $\frac{1}{70}$ to $\frac{1}{20}$ of a grain)—were taken daily for four weeks by young healthy men,[1] for experimental purposes. The most marked change that was afterwards noticed was persistent constipation; in several cases increased micturition and a sensation of burning in the urethra. In a few cases the pulse-rate rose considerably, whilst sudden attacks of palpitation of the heart and a feeling of nervous dread occurred repeatedly, especially on lying down. In the greater number of cases headache, at first lasting only a short time, but then becoming persistent for days together, rendered further investigation impossible. Bleeding from the nose occurred, without any assignable cause, in some of the subjects of this experiment. Painted on the unbroken human skin, cocaine is wholly inert, but it will act if the skin has been deprived of its epidermis. By dipping a broad electrode covered with flannel in a 10 and 20 per cent. solution of cocaine, and making it the anode of an electric current, we can in the course of a few minutes, by applying it to the unbroken skin, render the part insensible.[2] This depends upon the cataphoric action of the galvanic current, by means of which fluids are transmitted from the anode to the cathode. The stronger the current and the more concentrated the solution, the more complete is the anæsthesia.

According to the German Pharmacopœia the maximum single dose of cocaine hydrochlorate is 0·05 gramme ($\frac{3}{4}$ of a grain), the largest daily dose 0·15 gramme ($2\frac{1}{4}$ grains). Certain persons, chiefly those who are weak and anæmic, are peculiarly sensitive to cocaine. If it is necessary to administer a full dose to such persons with the view of producing local anæsthesia, it is advisable first to try the effect of a small dose, say 3 to 5 milligrammes ($\frac{1}{20}$ to $\frac{1}{13}$ of a grain).

Anyone who is in the habit of frequently prescribing cocaine will do well, for the reason previously stated, not to keep it in the solution, but to use the small compressed tabloids, which can now be procured from the various

[1] Hugo Schulz, 'Verhandl. d. med. Vereins zu Greifswald,' 1890, s. 6.

[2] Wagner of Vienna, according to W. Herzog, 'Münch. med. Wochenschr.,' 1886, s. 222—from v. Ziemssen's Clinical Institute.

pharmaceutical chemists. The tabloids are readily dissolved in a few drops of water. As they contain very little cocaine, they are made up with a little sodium chloride or sulphate. Other active remedies, such as morphine, strychnine, &c., may also be obtained in this form, which is not only convenient, but is one in which the remedies are not liable to undergo change.

VII.

Herba Lobeliæ—Properties and use—Aconitine—A glimpse into the past—Experiments of Matthiolus in the sixteenth century—Poisonous action—Uncertain composition of the aconitine of commerce—Its clinical application—Veratrine—Its effects—Internal and external use—Hellebore—Colchicum autumnale—A poison and a medicine.

Herba Lobeliæ, lobelia, from *Lobelia inflata, Indian tobacco,* belongs to the Natural Order *Lobeliaceæ;* the plant is gathered at the time of flowering, dried, and usually compressed into packets. It grows wild in the east of North America, and has been long used by the people as a medicinal plant. It was next employed by physicians, and thus about fifty years ago came to Europe.

Lobelia has an unpleasant burning and acrid taste. Its active constituent is a non-volatile alkaloid which can only be extracted by very careful manipulation, and even then it is only partly obtained in a crystalline form.

That *Lobelia inflata* possessed poisonous properties was well known in former times, as is reported by Wibmer.[1] Taylor mentions the case of a man who took 3·6 grammes (55 grains) of lobelia in one dose. Although the man vomited a considerable quantity he became unconscious, his pulse fell, the pupils were strongly contracted, the facial muscles were convulsed, and he died in thirty-six hours. At the post-mortem examination the mucous membrane of the stomach was found to be much inflamed.

The results of several experiments on the action of lobelia on animals have been published. I shall here

[1] Wibmer, Bd. iii, s. 234; Taylor, vol. iii, p. 379; Hagen, 'Die seit 1830 in die Therapie eingeführten Arzneistoffe,' Leipzig, 1863, ss. 550—554.

give substantially the latest account, which contains also references to previous authors.[1] Warm-blooded animals die after taking lobelia, from paralysis of the respiration; lobelia therefore belongs to the respiratory poisons. At first respiration is strongly stimulated, the volume of each single respiration being increased; whilst the energy, passing from the nervous centre to the respiratory muscles, is also greatly augmented. When the vagi are uninjured this result is more strongly marked than when they are divided. Stimulation of the vagus, after lobelia has been given even in rather small doses, does not produce an inhibitory action on the heart, nor does it excite contractions of the bronchial muscles.

The increased strength of the nervous impulses which, under the influence of lobelia, is developed in the respiratory centre must be of therapeutic importance. Practical experience has shown that preparations of lobelia are highly beneficial in cases of severe asthma.[2] The diversity of these preparations has hitherto rendered it difficult to make a definite statement with regard to the value of lobelia: either they contained nothing, or too little, or too much of the active agent, and consequently they produced either no result, or they developed poisonous symptoms. Until, therefore, lobelia is introduced in a definite and stable form we cannot depend upon its action, whether we administer the herb or its tincture, both of which at present are officinal. The largest single dose of the tincture is 1 gramme (15 grains), the largest daily dose being 5 grammes. The dose of lobelia itself is not fixed, as it is only used as a tincture. The latter is said to be effective only when it is prepared from the fresh plant in North America, consequently many physicans procure it direct from that country.

In this group of substances, the therapeutic action of which is uncertain, aconitine must be included. Aconitine is obtained chiefly from the tubers and leaves of *Aconitum napellus*, or monkshood, Natural Order *Ranunculaceæ*, that

[1] H. Dreser, 'Arch. f. exper. Path. u. Pharmak.,' 1889, Bd. xxvi, s. 237.

[2] S. Nunes, 'De la Lobéline dans la thérapeutique de l'Asthme,' Rio de Janeiro, 1889. Nine observations on patients under treatment with "lobeline," in doses 0·05 to 0·4 with adults, 0·01 to 0·05 with children.

grows wild in the mountainous districts of Europe, and is cultivated in gardens. Other species also contain it. The quantity of aconitine in the plant is said to be materially lessened by cultivation. When chemically pure it is white, does not crystallise easily, has a bitter taste and an alkaline reaction. Its composition is $C_{33}H_{43}NO_{12}$. It is easily soluble in ether, chloroform, and alcohol. When heated with acids it is decomposed, by the absorption of one molecule of water, into benzoic acid and another alkaloid, which has been called aconine ($C_{26}H_{39}NO_{11}$). Aconite and the allied species contain other alkaloids, the characteristics of which are, however, still uncertain, and have no particular medicinal interest.[1]

Aconite has been known as a poisonous plant from very ancient times: it was one of those commonly employed for this purpose by the Greeks; later on it was used in vivisection experiments conducted by the State, and in our own times it has occasionally caused death by being mistaken for other medicinal or culinary plants.

Cerberus, when dragged to the upper world by the Tirynthian hero, howled with rage and spat white foam upon the earth, out of which grew the poisonous aconite from which Medea prepared her poisons (Ovid, 'Metamorph.,' vii, 406). Matthiolus,[2] a physician of Siena, relates as follows:—In the year 1524, in the Capitol at Rome, an oil recommended by a professor from Bologna as an antidote for vegetable and animal poisons was tried by command of Clement VII on two robbers condemned to death. After the criminals had eaten some pastry mixed with aconite, the papal physicians rubbed one of them with the oil; he survived, though not without severe symptoms of poisoning. The oil was not applied to the other criminal, and he died with all the torments which "Avicenna (obiit 1037) had already described as belonging to aconite." Later, in 1559, an opportunity offered itself to Matthiolus of personally studying

[1] See also P. C. Plugge, 'Die wichtigsten Heilmittel in ihrer wechselnden chemischen Zusammensetzung und pharmakodynamischen Wirkung,' translated by E. Schär, Jena, 1886, ss. 1 bis 13.

[2] A. Matthiolus, 'Commentarii in sex libros Dioscoridis,' Venetia, 1565, p. 1095.

in Prague the effects of aconite on a thief condemned to the gallows. The imperial physicians were about to experiment with a secret remedy which had already saved the life of a condemned man, after two drachms of arsenic had been administered to him. "Lubens itaque devoravit ille lethiferum Napelli pharmacum, utpote qui non solum sibi conducibilius censebat, veneno in carcere necari quam laqueo publice in patibulo suspendi, sed quod etiam speraret se a nobis servari posse." When, after an hour and a half, there still was no symptom of poisoning, the physicians gave the criminal a fresh dose of a decoction of aconite which had been prepared with special care; the imperial commission waited with the man for two hours longer, but to no purpose. He was then taken back to his dungeon; the physicians weary with waiting withdrew, but the Italian, eager for knowledge, undertook the further observation of the experiment. An hour later the poison began to act, and Matthiolus was quickly summoned by the gaoler. He found the condemned man quite prostrate, incapable of holding himself upright, with a feeling of great oppression in the chest; cold sweat stood on his forehead; his pulse was hardly perceptible, though the man himself was perfectly conscious. Matthiolus gave him the antidote. The criminal, however, was quickly seized with convulsions of the ocular and facial muscles, opisthotonos, unconsciousness, diarrhœa, and vomiting, after which there was a return of consciousness, and the unhappy man felt somewhat easier. He then turned on his side as if to sleep, and died, his face turning blue, "ac si laqueo suspensus."

Matthiolus experimented with aconite upon yet another criminal sentenced to death, in order to try the effect of the Arabic medicine bezoar as an antidote. This, which at that time was held in high esteem, is a hard concretion obtained from the paunch of ruminant animals in the East, and is mixed with neutral organic compounds. The unfortunate wretch complained of the burning taste of the poison; he vomited, and felt as if a ball was present in the umbilical region, a sensation which caused a feeling of cold to spread upwards into his head. Stupor soon set in, followed by paralysis, first of the left, and then of the right side,

which was accompanied by giddiness, a general feeling of shivering, convulsions of the eyeball and of the mouth, violent pain in the upper and lower jaws, distension of the abdomen, burning thirst, delirium, an extremely variable pulse, intense cyanosis, and temporary blindness; but, notwithstanding all this, speech and consciousness were not lost. The tortured man, who was twenty-seven years of age, had, seven hours after taking the poison, apparently quite recovered, and of course the recovery was attributed to the action of bezoar.

I have repeated these stories here because, apart from their historical interest, they afford a true picture of poisoning by aconite, from which we may elicit some interesting facts which fully agree with those observed in some cases of poisoning of recent date.[1]

Soon after the poison has been taken a constricting, burning sensation is felt in the throat; in addition there is vomiting, contraction, and afterwards dilatation of the pupils, which in both conditions are insensitive to light; trismus, clonic spasms in the face, hands, and arms; difficulty of respiration, which at first forty in the minute, short and irregular, soon becomes very laboured. There is a feeling of great anxiety, with oppression in the cardiac region, whilst the pulsation of the heart is irregular, frequent, and scarcely perceptible. The mind is tolerably clear, but there is great sensitiveness to light, and much exhaustion. The hands feel heavy and cold. Alternating with this hyperæsthesia we notice transient blindness and deafness.

All regions are affected with the exception of the cortex of the cerebrum. Everywhere else there is a condition of irritation which passes into one of paralysis. Death is caused by paralysis of the heart and the respiratory centre.

On comparing the different accounts one or other symptom is frequently absent; but this need cause no surprise in the case of a poison which has so many different effects. Some details of its action may be masked by the greater prominence of others, according to the time which has elapsed since the drug has been taken. Moreover it must not be forgotten that different species

[1] A. Busscher, 'Berlin. klin. Wochenschr.,' 1880, ss. 337 und 356.

of aconite vary as to the quantity and quality of the alkaloids which they contain; and finally that not even what in commerce has hitherto been call' aconitine is a uniform or chemically pure substance. In Europe alone, the aconitine of almost every manufacturer has its own composition. In general the aconitine of commerce is a mixture of chemical compounds obtained from the plant.

This sufficiently accounts for the variations in the results of the numerous experiments which have been made on animals with aconitine, and which here and there reach such a point of subtlety that it would be difficult to see our way clearly, even if we were dealing with a uniform and chemically pure poison. How far this is from being the case we may learn from the sad poisoning case in Winschoten in Holland.[1]

Dr. C. Meyer of that town had prescribed for a patient a solution of nitrate of aconitine in alcohol, of which he was to take twenty drops from time to time. Hitherto the chemist had kept a German preparation, which he had replaced, when the supply fell short, by a French one with a similar name. The German aconitine had been frequently used by Dr. Meyer without any bad results; but the patient was so violently affected by the drug that the physician was hurriedly summoned. In order to prove that the strange and sudden change for the worse could not be caused by the solution of aconitine which he had prescribed, Meyer took fifty or sixty drops of it in the presence of the patient's friends. Notwithstanding the fact of his having, as it chanced, taken the aconitine on a full stomach, symptoms of poisoning soon set in, and he died five hours afterwards. It was proved, when the matter came before a court of law, that the unfortunate physician had only swallowed about 0·004 gramme (about $\frac{1}{17}$ of a grain) of nitrate of aconitine.

Plugge and Huizinga of Groningen were commissioned to investigate the pharmacology in this case. In the course of their investigations[2] they discovered—and this has a

[1] See A. Busscher, loc. cit.

[2] Plugge, "Inter. Med. Congress," London, 1881, vol. i, p. 472, 'Arch. d. Pharmacie,' 1882, Bd. ccxx, s. i.

bearing with regard to the effect of nitrate of aconitine on frogs and warm-blooded animals—that the salt extracted by Petit in Paris was eight times as strong in its poisonous action as that extracted by Merck in Darmstadt; that the latter was at least twenty to thirty times stronger than that of Trommsdorf in Erfurt; so that the French nitrate of aconitine was at least one hundred and sixty times more poisonous than the Thuringian drug!

After this nothing more need be said at present about the absolute value of the earlier experiments on animals. In order to demonstrate roughly the qualitative action of most kinds of aconitine, I have just injected into a vigorous frog 0·0065 gramme of German hydrochlorate of aconitine.

The ventricle which is exposed is beating forty-five times in the minute. Within the next five minutes the number of beats rises to 50, 60, and 70, and then quickly falls. Fifteen minutes after the injection the number has sunk to 30, twenty minutes afterwards to 14, whilst a few minutes after the ventricle is brought to a standstill in a condition of moderate diastole, though the auricles still go on working.

Respiration ceases a few minutes after the injection, whilst the eyes are closed and the head hangs down, and when placed on its back the frog remains in that position. Sensory stimulation evokes neither reflex nor voluntary motion. Sometimes the frog turns over vigorously and leaps forwards, but this, too, soon becomes impossible.

I now give a rabbit the same amount of hydrochlorate of aconitine as I gave the frog. In five minutes the respiration begins to be irregular and becomes laboured, the animal opening its mouth wide and using all the accessory muscles of respiration. The heart beats so rapidly that its pulsations cannot be counted. This is followed by spasms of the muscles of the jaws, whilst the respiration quickly becomes more and more laboured, and death takes place seven minutes after the injection, accompanied by the general spasms of asphyxia. If the heart is immediately exposed, it will be seen to be still acting, but feebly and spasmodically.

Sudden paralysis of the respiration, followed by paralysis of the heart, is the chief poisonous result due to the action

of aconitine. Both these results give rise to the difficult respiration, cyanosis, and general convulsions in the case of warm-blooded animals. The frog is not affected in the same degree because its nervous system can bear paralysis both of the heart and of respiration without convulsions being induced. It has been proved, however, that in this animal paralysis of the motor nerves of the striated muscles is brought about by this poison just as it is with curare. It may occur also in warm-blooded animals, but, as a rule, the rapid termination by asphyxia, due to paralysis of the respiratory centre, gives no time for its development.

The muscles, as Plugge[1] has shown with various kinds of aconitine, do not lose their excitability.

Aconite was introduced into therapeutics by Stoerck of Vienna in 1762. Its preparations are seldom made use of in Germany, but in other countries—as, for example, in England —they are still employed. Its use has been highly recommended in all kinds of fever. Owing to the uncertain strength of aconitine, it is of course intelligible that nothing very definite can be said as to its therapeutic use. Any statements of the kind must, as yet, be accepted with reserve.

It is true that aconite diminishes the frequency of the pulse and lowers the arterial tension, but even if it simultaneously lowered the temperature—which it does not—its employment is not desirable, for the same results can be obtained by means of much less dangerous remedies.

It may, however, sometimes be used to diminish excessive sensibility of the peripheral nerves.

In experiments upon human beings it has been noticed that aconite has a peculiar influence over the peripheral nerves; it causes a decrease of sensibility in cases of twinging and tension of the trigeminal nerve, and also where there is a tingling or numbness in the nerves of the extremities. This result points to the fact that aconite acts upon these nerves, and possibly causes a change in their irritability similar to that which the constant current brings about. Trustworthy reports have been published of cases of trige-

[1] M. Murray, 'Philadelphia Med. Times,' 1879 (printed separately); Langgaard, 'Arch. f. pathol. Anat.,' 1880, Bd. lxxiii, s. 229; Plugge, ibid., 1882, Bd. lxxxvii, s. 410.

minal neuralgia, of sciatica, &c., which resisted all other methods of treatment, but were either benefited or cured by the administration of this drug. In such cases, therefore, we may use aconitine with advantage, cautiously beginning with very small doses ($\frac{1}{10}$ milligramme, *i. e.* $\frac{1}{660}$ of a grain) and gradually increasing them. Gubler reported that cases of trigeminal neuralgia, where the resection of a branch of the nerve had no effect, have been known to improve at once when doses of 0·0005 gramme ($\frac{1}{133}$ of a grain) were administered.[1]

Only aconite root and the tincture prepared from it are included in the German Pharmacopœia. In former editions the maximal dose of aconitine was 0·0004 gramme ($\frac{1}{166}$ of a grain).

Veratrine is a light white powder, only slightly soluble in boiling water; the solution has a sharp taste, and slowly turns litmus paper blue. Veratrine is soluble in four parts of alcohol and two of chloroform, and is less soluble in pure ether. These solutions have a strongly alkaline reaction. Dilute sulphuric or hydrochloric acid gives a bitter acid solution.

Veratrine is obtained from the seeds of *Schœnocaulon officinale*, Cevadilla, belonging to the Nat. Ord. *Melanthaceæ*, a native of Mexico. The roots of *Veratrum album* and of *Veratrum viride* do not, as was formerly supposed, contain veratrine, but chiefly two other alkaloids,[2] jervine ($C_{27}H_{47}N_2O_3$) and veratroidine ($C_{24}H_{37}NO_7$). Commercial veratrine is mainly composed, with other things, of the alkaloids found in cevadilla. Meisner, an apothecary of Halle, discovered veratrine in 1819, and in his description of it in 1821 was the first to use the word "alkaloid." In the pure state veratrine has the formula $C_{32}H_{49}NO_9$. Though veratrine is odourless, the smallest possible quantity placed in the nostril brings on a violent fit of sneezing. It is quite sufficient merely to smell the powder. Veratrine produces intense

[1] Gubler, ref. 'Centrabl. f. d. med. W.,' 1887, s. 367; Seguin, 'Medical Record,' New York, 1879, January 4th.

[2] Wright and Luff have found five in the first and six in the latter, 'Journ. Chem. Soc.,' 1879, 35; ref. to Schauenstein, s. 700. Particulars may be seen in the works of G. Plugge and Schär, s. 112.

itching in the palate, and if brought in contact with the respiratory passages will set up coughing. It causes a burning pain when it touches the broken skin or if it is injected subcutaneously. If rubbed into the skin in the form of an ointment or an alcoholic solution, it brings on a burning, pricking sensation, and increases the sensibility; this is followed by numbness, and sometimes by inflammation.

After taking a centigramme, or less, of veratrine a sensation of warmth is experienced in the stomach, which soon becomes of a burning character; later on, violent vomiting, griping, and diarrhœa appear, and the vomited matter may be mixed with blood. This irritability of the stomach and bowels occurs also when veratrine is applied subcutaneously.

Twenty minutes ago I injected a powerful *Rana temporaria* under the skin of the back with 0·00005 veratrine dissolved in a little water and a trace of alcohol. The animal is now quiet, lies on its back when placed there, but can still jump vigorously. Twenty minutes later it is unable to spring, but crawls clumsily and with difficulty. The muscles obviously take more time to contract and to return to the normal condition of relaxation. Fibrillar contractions are seen in the anterior muscles of the thigh. If I irritate the animal with a needle when it is placed in a sitting posture it responds at once, and makes violent attempts to jump, but ends with its hind legs extended as in tetanus. Respiration is 80 a minute, the heart-beat 50, and both are obviously excited; this is especially noticeable in the energetic contractions of the ventricles.

A further injection of 0·0001 of veratrine paralyses the animal; it lies upon its belly, and only responds as before when a strong stimulus is applied to the nictitating membrane of the eye. Respiration becomes shallow and infrequent, but the heart still beats strongly; the pupils are dilated. With a repetition of the same dose respiration ceases, but the heart beats on strongly for a time, though only at the rate of 36 per minute.

The changes in the motor apparatus have been more closely analysed, and the various details established.[1]

[1] Kölliker, 'Archiv f. pathol. Anat.,' 1856, Bd. x, s. 257; v. Bezold und Hirt, 'Unters. aus d. Würzb. physiol. Labor,' 1869, s. 1; Fick u.

If we commence with a very small dose, veratrine affects THE HEART as follows :—At first there is a continuous stimulation and increase in the pulse-rate and in the blood-pressure. The duration of the contractions then becomes longer and longer, the rate being diminished to one half owing to the duration of the systole. All parts of the heart finally become insensitive even though it still contracts occasionally. Atropine now produces no effect. The pulse-rate and blood-pressure gradually become less and less, and if artificial respiration has been maintained death takes place from paralysis of the heart.

The RESPIRATORY CENTRE is first of all stimulated and then paralysed by veratrine. Paralysis of the cortex of the brain only occurs when there is not a sufficient supply of arterial blood, and owing to this consciousness is maintained for a relatively long period of time.

Veratrine is rarely used internally for therapeutic purposes, for though it has been proved to be an antipyretic,[1] it produces other collateral effects which destroy its value. These are vomiting, bloody diarrhœa, muscular convulsions, and other signs of irritation which soon bring about a condition of collapse. Externally veratrine is still in use in the form of an ointment or in alcoholic solutions for neuralgic cases. It may be that its action—which often is unmistakable—is due to a transitory though direct paralysis of the affected nerves.

Owing to its poisonous properties 0·005 gramme ($\frac{1}{13}$ of a grain) is the largest dose of veratrine that may be dispensed in Germany unless the sign (!) is added, showing that the dose is specially ordered.

COLCHICUM AUTUMNALE, meadow saffron, is one of the autumn-blooming Colchiceæ, has a purple or lilac flower, and belongs to the Nat. Ord. Melanthaceæ. It was

Böhm, 'Verhandl. d. physik. med. ges. Würzburg,' Bd. iii, s. 198; Rossbach und Schüler, 'Archiv f. d. ges. Physiol.,' 1876, Bd. xiii, s. 607; 1877, Bd. xv, s. 1; 1880, Bd. xxi, s. 240.

[1] Th. Kocher, 'Behandlung der croupösen Pneumonie mit Veratrum-Präparaten,' Würzburg, 1866; Liebermeister, in v. Ziemssen's 'Sammelwerk,' 1876, Bd. ii, s. 230; Pégaitar, 'Arch. f. klin. Med.,' 1869, Bd. vi, s. 156.

considered to have poisonous properties in former times; during the last century, on the recommendation of Stoerck, it was included in the list of drugs, but at the present time it is—with good reason—not very frequently prescribed in Germany. The whole plant contains colchicine, which is a weak basic crystalline body, of which the probable composition is $C_{22}H_{25}NO_6$.[1]

Most of the cases of poisoning by colchicum occur from the seeds being eaten by children. Several hours may elapse after the seeds have been taken before the colchicine is liberated in sufficient quantity to cause poisonous symptoms. It belongs essentially to the class of acrid narcotics; vomiting and colic, spasms of the muscles of the face, trunk, and limbs, difficulty of respiration, cyanosis, slightly dilated pupils, turgid abdomen, frequent and small pulse, violent diarrhœa and collapse being, according to the reports given in medical works, the chief effects which are produced.[2]

Rossbach, in experiments upon animals, found that colchicum is a slow but very effective poison.[3] Its action is strongest on the carnivorous, considerably less upon herbivorous, and least upon cold-blooded animals. It first excites and then paralyses the central nervous system; the stage of excitement need not, however, occur. The paralysis affects the brain and spinal cord, the motor nerves and striped muscles are unaffected; so is the heart at first, but it becomes implicated later simply by the accumulation of carbonic acid in the blood. The mucous membrane of the stomach and intestines is swollen, and extravasation of blood takes place into the bowels. There is strong hyperæmia of the kidneys. Death results from direct paralysis of the respiration.

Later researches[4] have amplified our knowledge as follows:—Colchicine may be converted by means of active

[1] M. Hübler, 'Jena'sche Zeitschr. f. Med. und Naturw.,' 1864, Bd. i, s. 247; P. Hertel, ref. 'Berichte deutsch. chem. Ges.,' 1881, Bd. i, s. 1411.

[2] Krahmer, 'Journ. f. Pharmakodyn.,' 1858, Bd. ii, s. 560.

[3] Rossbach, 'Pharmakolog. Untersuchungen,' Würzburg, 1876, Bd. ii, ss. 1—59.

[4] C. Jacobj, 'Arch. f. exper. Path. u. Pharmak.,' 1890, Bd. xxvii, s. 119.

oxygen into oxydicolchicine $(C_{22}H_{25}NO_6)_2O$. It undergoes the same change in warm-blooded animals. Pure colchicine has but little effect upon frogs, whereas oxydicolchicine in doses of 1 cg. acts on them in a similar manner to veratrine. Both act in the same way on warm-blooded animals, giving rise to violent irritation of the bowels (gastro-enteritis) and to loss of sensation and muscular power. Again, an ascending paralysis affects the motor centres of the medulla oblongata and spinalis, and death occurs from paralysis of the respiratory centre.

The pharmaceutical chemist F. Ratti, of Rome, describes an epidemic of poisoning which took place in 1875.[1] This epidemic broke out in a certain quarter of Rome. Its symptoms were catarrh of the stomach and bowels, with vomiting, colic, and quickened respiration, which were accompanied by a slow pulse and reduced temperature. It was ascertained that the cause of this outbreak arose from goat's milk which was obtained from a certain source. The milk did not contain any inorganic poison, for the goats were found to be healthy, but Ratti examined their pasture ground, and found that the goats had eaten *Conium maculatum*, *Clematis vitalba*, and *Colchicum autumnale*, which grew there. He further discovered that the milk contained colchicine, which must have passed into it from the stomach and through the vascular system of the animals.

It is pretty generally agreed that colchicum poisoning may run on insidiously for several days, and that after a deceptive remission the symptoms may again become aggravated. The diagnosis can only be made from the history of the case, and by portions of the plant being found in the vomited matter.

Up to the present time preparations of colchicum have been frequently used for the treatment of gout and rheumatism, and in medical practice considerable reliance has been placed in them. There is, however, considerable doubt as to their efficacy. In the first place the Tinctura Seminis Colchici and the Vinum Seminis Colchici are almost always given together with tincture of opium, and consequently it is impossible to state positively whether the decrease of pain in

[1] 'Das Ausland,' Leipzig, 1875, s. 964.

rheumatic cases is due to a specific action of the colchicum, or to the sedative effect of the morphine. The positive harm which colchicum causes in acute articular rheumatism is known, namely, violent diarrhœa. This compels the patient constantly to move his limbs, which are acutely inflamed and sensitive, and his strength is thus doubly wasted. At the present time we possess in sodium salicylate, antipyrin, and similar medicines, remedies against rheumatism and gout, which are efficacious in a much higher degree than colchicum, and which, moreover, are free from its irritating and dangerous properties.

VIII.

Amyl nitrite—Its action upon the cerebral vessels—Upon the blood-pressure and heart—Its use in spasm of the vessels—Alleged disadvantages of the drug—Artificial diabetes produced by its use—Methæmoglobin appears after prolonged use—Sodium nitrite—Nitro-glycerine.

Chemistry has introduced to our notice a nerve-depressor of a peculiar nature, viz. amyl nitrite—a clear volatile liquid having a yellowish colour, a peculiar, not disagreeable odour resembling that of over-ripe pears, and a burning aromatic taste. It is scarcely soluble in water, but is miscible in all proportions and under all conditions with alcohol and ether; it boils at 97°—99° C. (about 206° to 210° F.), has a sp. gr. of 0·87 to 0·88, and when ignited burns with a yellow luminous though smoky flame.

Amyl nitrite was first discovered by Balard in 1844. It is produced by passing nitrous acid, obtained by warming nitric acid and starch, into amyl alcohol. The action is as follows:

$$HNO_2 + C_5H_{12}O = C_5H_{11}NO_2 + H_2O.$$

Amyl nitrite is thus $C_5H_{11}.NO_2$, a neutral acid ether or ester. In the German Pharmacopœia it is called Amylium Nitrosum. The name occasionally given to it of Amylenum Nitrosum is chemically incorrect, for it contains no amylene, C_5H_{10}.

The chemist Guthrie seems to have been the first to draw attention to the effects of amyl nitrite, namely, that when inhaled it causes flushing of the face, throbbing of the carotids, and quickening of the heart's action.

Later on Sir B. W. Richardson and Dr. A. Gamgee discovered that in animals amyl nitrite dilates the capillaries and

lowers the arterial tension. This observation induced Lauder Brunton in 1867 to try an experiment on a case of angina pectoris in the Edinburgh Infirmary.[1] The experiment, as was expected, was successful. "Simultaneously with the flushing of the face the pain completely disappeared, and generally did not return till its wonted time next night. Occasionally it began to return about five minutes after its first disappearance, but on giving a few more drops it again disappeared, and did not return."

The action of amyl nitrite is in general most readily demonstrated on human beings. Here is a sealed glass tube in which there are three drops of the ether. I break it in a handkerchief and inhale its vapour. In ten to fifteen seconds I am sensible of the beating of my carotids, and, by means of my watch, I ascertain that my pulse has risen from 75 to about 95; my whole head has become warmer, and my face and ears are a deep red.

In a previous experiment[2] I gave a man, who was naked and standing upright, five drops to inhale. The flush on the face soon extended over the whole neck, and numerous red spots of irregular size appeared on his chest; these became gradually larger, and finally coalesced. This condition extended on the right side to the lower limit of the liver, and on the left side to the region of the stomach. From this point the dilatation of the vessels spread, causing a reddish mottling on both sides of the abdomen, but leaving the region round the umbilicus free. About the groin the redness was less distinct, though still clearly visible, and formed small isolated spots. It did not extend beyond this region, and it disappeared as quickly as it came.

Respiration was more frequent and deeper, and felt freer to the patient.

If an individual inhales a second or third dose of about five drops of amyl nitrite, he experiences, in addition to the accelerated action of the heart and the dilatation of the arteries in the upper parts of the body, a feeling of intoxi-

[1] Lauder Brunton, "On the Use of Nitrite of Amyl in Angina Pectoris," 'Lancet,' 1867, vol. ii, p. 97; "Pharmaceut. Journ.," December 22nd, 1888.

[2] R. Pick, 'Arch. f. klin. Med.,' 1876, Bd. xvii, s. 128.

cation and dizziness and of general relaxation of the muscles; later on unconsciousness is liable to supervene from the cumulative effect of the doses.

The temperature—taken in the rectum—falls a little in these inhalations, as can be proved by the thermometer.[1] The fall is probably due to the increased loss of heat from the skin, owing to a larger amount of blood being present in the cutaneous vessels, and is more marked in febrile than in normal conditions.[2]

It is remarkable that, according to the ophthalmoscopic observations made by Saemisch on my pupil R. Pick, amyl nitrite does not affect the arteries of the retina, though the arteries of the head are distinctly dilated. The capacity of the lungs is not appreciably altered by the inhalation of the drug.[3]

Amyl nitrite paralyses the coats of the arteries independently of the vaso-motor centre in the medulla oblongata, for by blowing it into the lungs of an animal whose spinal cord has been divided in the cervical region, still further dilatation of the blood-vessels is brought about than existed previously, when the connection of the vaso-motor centre was cut off from the blood-vessels of the greater part of the body.

If the arteries which go to the brain are ligatured or clamped this organ is temporarily paralysed, and amyl nitrite if inhaled can have no access to or effect upon the vaso-motor centre; nevertheless if it is now blown into the lungs it produces just the same result as before, and the blood-vessels of the body become fully dilated.

We must, therefore, conclude that it acts by some peripheral mechanism either in the spinal cord or the walls of the blood-vessels, and thus influences the calibre of the vessels without the intervention of the medulla oblongata.[4]

If we divide all the nerves connected with any part of

[1] H. Arntz, 'Arch. f. d. ges. Physiol.,' 1883, Bd. xxxi, s. 539.

[2] N. Sassezki, "Ueber die Wirkung des Amylnitrits auf die Körpertemperatur" (aus Manassein's Klinik), 'St. Petersburger med. Wochenschr.,' 1879, s. 392.

[3] R. Pick, 'Ueber das Amyl Nitrit,' Berlin, 1877, 2 Aufl. (Doctor-dissertation aus dem Pharmakol. Institut zu Bonn.)

[4] Sigm. Mayer, 'Corr.-Blatt deutscher Aerzte,' in Prag, 1875, No. 24.

the body which is under the influence of amyl nitrite, and at the same time divide the spinal cord in the cervical region, we shall then see that the drug still produces an effect upon the vessels of that part.

That its action is peripheral and exerted upon the walls of the blood-vessels is supported by the fact, that the vapour of amyl nitrite quickly paralyses isolated smooth muscles and the contractile protoplasm of the lower organisms; and, moreover, if amyl nitrite is inhaled after clamping one of the carotid arteries, it does not alter in the slightest the calibre of the blood-vessels of the ear on that side, whereas if the sympathetic is cut after the artery is clamped, the vessels of the ear, which previously were collapsed owing to the clamping, very quickly and distinctly dilate.

Filehne holds that the paralysing action of amyl nitrite is exerted chiefly upon the vaso-motor centre in the medulla oblongata.[1] This centre may be acted upon as well, but the paralysis seems to be, on the contrary, chiefly of a PERIPHERAL character.[2]

The blood-pressure falls at once on inhaling amyl nitrite, but it falls much less, if at all, when in animals the spinal cord being divided and the vessels in the trunk and extremities thereby dilated, the abdominal aorta is simultaneously compressed. It follows from this that the fall of the blood-pressure is not due to a weakening of the heart's action.

In human beings THE FREQUENCY of the heart's action is very distinctly INCREASED by nitrite of amyl, and this is due to the sudden fall of blood-pressure consequent on the dilatation of the blood-vessels. The normal blood-pressure acts as a stimulus upon the vagus centre and maintains its "tone." This stimulation and tone are lessened with the fall of the blood-pressure, and the inhibition of the heart

[1] Filehne, 'Arch. f. ges. Physiol.,' 1874, Bd. ix, s. 470; 'Arch. f. Anat. u. Physiol.,' 1879, s. 385.

[2] Lauder Brunton, 'Abdruck a. d. Ber. der math. phys. Classe der Königl. Sächs. Ges. d. Wissensch.,' Leipzig, 1869; 'Journal of Anat. and Physiol.,' vol. v, p. 92; Eulenburg und Guttman, 'Arch. f. Anat. und Physiol.,' 1873, s. 442; O. Amez-Droz, 'Etude sur le Nitrite d'Amyle,' Doctor-Diss., Bern, 1875.

being partly lessened, the number of its contractions increases. Thus, the inhalation of amyl nitrite and its indirect action upon the heart give us one of the best examples of the *mutual* relationship which exists between the vagus and the arterial pressure, and of the way in which they control each other. The nerve withdraws its inhibitory power to a certain extent, otherwise the heart would continue to beat at the same rate, and consequently the blood-pressure would sink lower than it had done from the dilatation of the blood-vessels. The cessation or diminution of this inhibitory action, however, is brought about by a fall of blood-pressure. The heart then itself at once furnishes the necessary compensation by its more rapid action.

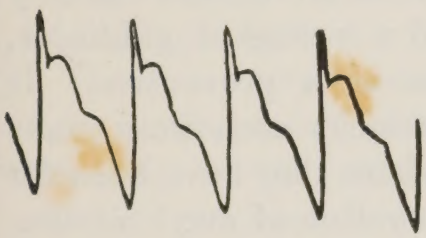
Again, the increased activity of the respiration which is brought about by amyl nitrite is said to be due to an excitation of the respiratory centre arising from intrinsic changes in the circulation and distribution of the blood, and probably also to a larger supply of blood being furnished to the ganglionic cells.

We may mention—on account of his name being so well known—that Charles Darwin considered the flushing of the face brought about by the use of amyl nitrite to be similar, "in nearly every respect," to the blushing which occurs from emotion.[1] The comparison, however, cannot be carried any further, for Sir J. Paget has observed that even in women, who blush very readily, the dilatation of the vessels does not, at most, extend beyond the clavicles or scapulæ, whereas in the case of amyl nitrite, both in human beings and in animals, it extends over the trunk.

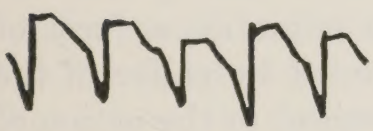
After this description of the characteristic properties of amyl nitrite it is obvious that it can be employed beneficially in a variety of disorders. Numerous medical and clinical reports have been published showing that whenever a morbid contraction of the arteries has been diagnosed as the cause of the disorder, or whenever this condition is present as a complication, the administration of nitrite of amyl is, as a rule, always indicated.

[1] Ch. Darwin, 'The Expression of the Emotions in Man and Animals,' 1872, p. 325.

Angina pectoris, *stenocardia,* a very painful neurosis of the heart, is in its spasmodic form quickly benefited and relieved by amyl nitrite, whilst it frequently resists most obstinately all other remedies. I here show you some sphygmographic tracings of the pulse [1] which clearly demonstrate the condition of the radial artery both before and during an attack as well as before and during the use of amyl nitrite.

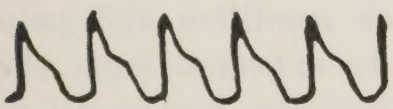


Tracing of normal pulse.

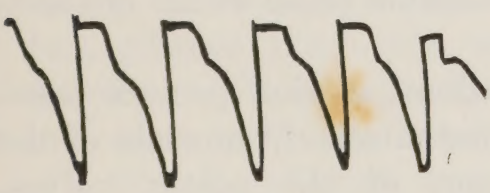


Tracing during the attack.

Severe pain in the cardiac region.



Pain temporarily relieved by the use of AMYL NITRITE.



Pain completely relieved by AMYL NITRITE.

You see that the artery during the attack is so contracted and tense that it hardly raises the lever of the instrument, and further that under the influence of the drug the artery quickly recovers its normal pliability.

The three last curves were taken within a few minutes of each other—the instrument being kept undisturbed on the radial artery.

Amyl nitrite has also been tried in epilepsy, and it has

[1] Lauder Brunton, reprint from the 'Reports of the Clinical Society,' London, 1870.

been successful in PREVENTING attacks in cases which were probably due to cerebral anæmia dependent upon arterial spasm—the advent of which is perceptible by the patient. This is the case when there is the so-called aura—that is, a sensation of cold or tingling in the extremities preceding the attack—which is due to the commencing arterial spasm, and which quickly extends to the cerebral vessels. When the attack has once commenced amyl nitrite is of no service. In other cases a characteristic aura does not occur; the only warning may be slight headache and a feeling of giddiness, and in these also amyl nitrite acts as a preventive. It has been further noticed that the attacks sometimes come on with increased violence in cases where they have been for some time warded off by the administration of amyl nitrite.

Among other diseases upon which this remedy has exerted a beneficial effect I may mention migraine, a form of trigeminal neuralgia which is accompanied by pallor of the face, and also painter's colic. With regard to the action of amyl nitrite upon lead colic the exhaustive researches of Riegel and Frank[1] have shown that it quickly diminishes the abnormal tension of the pulse, and renders the artery easily compressible. With this latter condition the pain disappears, but it returns—as must be expected from the nature of the disease—with a return of the high tension. The sphygmographic tracings resemble those which are seen in cases of angina pectoris.

We may here also include asthma, angina pectoris associated with valvular or other heart mischief,[2] anæmia of the brain resulting from insufficiency of the aortic valves, syncope during the administration of chloroform, and ordinary fainting fits; in all these and similar conditions[3] the effect of the remedy is to produce a diminution of the anæmic state of the brain, and an improved action of the heart and increased activity of the respiration.

[1] A. Frank, "Ueber die Veränderungen am Circulationsapparat bei Bleikolik," 'Arch. f. klin. Med.,' 1875, Bd. xvi, s. 423; Riegel, ibid., 1878, Bd. xxi, s. 201.

[2] E. Ungar, 'Berl. klin. Wochenschr.,' 1884, s. 693 (a very instructive case).

[3] See R. Pick's 'Monographie,' 1877, ss. 39—68.

After all, it must be said that in the light of our present experience, amyl nitrite deserves to be utilised more frequently by the physician than is at present the case. Its alleviating effects in suitable cases are unsurpassed in certainty. I think that its relatively infrequent use is due to the difficulty in administering it; for if exposed to the air it evaporates so quickly that it is almost impossible to give an exact and proper dose, whilst if a patient is allowed to inhale the amyl nitrite from an open bottle he may easily take an overdose.

These inconveniences may be avoided by ordering the drug in the small patent bottles recently introduced into Germany, or still better by using the sealed glass tubes, each of which contains about three drops. The patient breaks the tube in his handkerchief, and, holding this lightly in front of his mouth and nose, inhales the vapour.

The disadvantages and dangers in the use of amyl nitrite have been the subject of much discussion.

We may mention first the visual disturbances. The patients whom Sander treated with the drug stated that for some time after an inhalation everything appeared yellow. Schröter noticed a diminution in the field of vision, but this became normal on discontinuing the remedy.[1] The same observer has pointed out that the use of the drug sometimes caused delirium, and that in patients suffering from mental derangement there was an increase in, or return of, the delirium. Visual hallucinations and the hearing of sounds and voices were also noted. Samelsohn describes the case of a woman suffering from spasm of the eyelid to whom he gave amyl nitrite. After the usual effect of the inhalation had passed off the woman became pallid, deep spasmodic inspirations, cool skin, cold perspiration, and a small, thready, and extremely slow pulse were observed. This condition lasted for the space of an hour. The spasm of the eyelid disappeared, and only returned after thirty-six hours. Samelsohn mentions some conditions which contributed towards the development of these poisonous effects; in the first place, the administration of the drug, being

[1] Schröter, 'Zeitschr. f. Psychiatrie,' 1875, Bd. xxxii, s. 527.

from a bottle, was not under control; and further, the catamenia were present, and therefore the relaxation of the blood-vessels, in his opinion, must have been greater than usual.[1]

We may mention in passing that—as is the case in other instances where a dilatation of the blood-vessels is brought about—artificial diabetes may be produced in rabbits by the subcutaneous injection of amyl nitrite.[2] As far as I know, such a result has not been observed in the case of human beings, for here the action of the drug is not so violent, and does not last long enough. If amyl nitrite is swallowed, it does not appear to be poisonous, as might be supposed from its action, when it is inhaled by the lungs.[3]

If a dog is made to inhale amyl nitrite for some time, the harmless symptoms previously described appear; soon, however, in addition to the unconsciousness already induced, the body becomes restless, and respiration—which at times ceases—is deep and very irregular; finally it remains stationary for some time at the end of inspiration, and then, preceded by the well-known clonic spasm of the diaphragm, ceases. The convulsions due to suffocation need not occur, or only to a very slight extent. It has been shown in the case of other animals (rabbits) that these convulsions have their origin in the brain centres, and are independent of the spinal cord.[4] This view is supported by the fact that the muscles of the face are those first affected.

If we take a small quantity of blood from an animal dying in the manner just described, we find that it is slightly brown in colour, and the spectroscope shows a band in the red in addition to the two oxyhæmoglobin bands,—that is to say, a portion of the oxyhæmoglobin has been converted into methæmoglobin—an important toxicological substance to which

[1] Samelsohn, 'Berliner klin. Wochenschr.,' 1875, ss. 332 u. 349; G. C. Harlan, "Obstinate Blepharospasm cured by Inhalation of Nitrite of Amyl," 'American Journ. Med. Sc.,' 1877, vol. cxlvi, p. 411.

[2] F. A. Hoffmann, 'Arch. f. Anat. Physiol. und wissensch. Med.,' 1872, s. 746.

[3] J. Roesen, 'Centralbl. f. klin. Med.,' 1889, s. 777.

[4] S. Mayer und J. Friedrich, 'Arch. f. exper. Pathol. und Pharmakol.,' 1875, Bd. v, s. 55.

I shall have to refer in connection with potassium chlorate. Methæmoglobin neither absorbs oxygen when shaken with air, nor gives it up to the tissues, and consequently is of no further service in the animal economy.

The animal obviously dies from direct paralysis of the respiratory centre. Changes in the blood occur at the same time, and it is probably on account of these changes that artificial respiration fails, as I have myself witnessed, to keep the animal alive if we continue to administer amyl nitrite.

This poisonous action of large doses of amyl nitrite, if it is cautiously and properly given to human beings, need cause no anxiety, either on theoretical or other grounds, for up to the present time no fatal case of poisoning seems to have occurred.

The purity of amyl nitrite is sufficiently provided for in the Pharmacopœia, but if any doubt should exist, the tests mentioned there can be applied. The drug must be kept in the dark with a few crystals of potassium tartrate added to it, in order that this may combine with any free acid which is given off. The corresponding potassium salt and the acid tartrate of potassium are formed.

The similarity of the action of amyl nitrite with that of NITRITES in general has become more and more evident. A. Gamgee has shown that if amyl nitrite is added to blood the same colour change takes place as is the case with the metallic nitrites.[1] I have myself shown that sodium nitrite acts as a narcotic poison on animals.[2] The Spiritus Ætheris Nitrosi acts upon the blood-vessels, as well as in angina pectoris, in the same way as nitrite of amyl.[3]

Five minutes ago I injected 0·03 gramme ($\frac{9}{20}$ of a grain) of sodium nitrite, dissolved in a little water, under the dorsal skin of this vigorous Esculenta. The animal is quiet already, and a few minutes later it has become quite apathetic, its eyes are closed, and its head hanging down. If now I pinch its toes it wakes up for a time, lifts its head, opens its eyes, and endeavours to escape; but the move-

[1] A. Gamgee, 'Trans. Roy. Soc. Edinburgh,' 1868, pp. 589—625.

[2] C. Binz, "Ueber einige neue Wirkungen des Natriumnitrits," 'Arch. f. exper. Path. und Pharmakol.,' 1880, Bd. xiii, s. 133.

[3] D. J. Leech, 'Practitioner,' 1883, October, p. 241.

ments of its limbs are sluggish and incomplete, and it goes to sleep again directly. In the meantime the respiratory movements of the flanks, and underneath the lower jaw continue in full activity for some time. If the heart is laid bare, it is seen to be beating at the rate of forty a minute; but soon the paralysis increases, respiration is brought to a standstill, and all other movements cease.

If I now decapitate the animal, its trunk remains limp; even irritation of the spinal cord with a needle, or the application of acetic acid to the toes does not produce the slightest movement.

The paralysis soon descends, and the exposed sciatic nerve, as well as the muscles generally, lose their electrical excitability.

If I had tied the artery of one leg previously to the experiment, the sciatic nerve of that leg would have retained its excitability longer than the nerve on the other side; the poison, therefore, is carried by means of the blood, and directly paralyses the nerve, or more correctly its end-organs.

Again, if I were to leave the blood-vessels of the animal untouched, but to cut one of the sciatic nerves, the peripheral portion would remain sensitive longer than the uncut nerve. The poison, therefore, acts upon the brain, causing paralysis of the nerve-tissue there, which spreads downwards.

If the animal is killed by excising the heart at the commencement of the narcosis, the blood when diluted with water and examined spectroscopically shows the two bands of oxyhæmoglobin unchanged, and no other band in the red. The formation of methæmoglobin also takes place later in the frog. As this animal, however, can live for a considerable time without breathing, it is obvious—apart from the above-mentioned examination of the blood—that the paralysis is independent of the asphyxia. The paralysis is caused directly by the action of the nitrite upon the nervous centres. This is placed beyond doubt by the fact that when sodium nitrite is injected into a frog in which the blood has been replaced by a standard salt solution, exactly the same results are obtained.[1]

[1] C. Binz, "Narcotische Wirkungen von Hydroxylamin und Natriumnitrit," 'Arch. f. pathol. Anat.,' u. s. w., 1889, Bd. cxviii, s. 121.

The TRANSITORY NATURE of this paralysis of the brain may easily be shown by means of sodium nitrite. If we inject half the dose mentioned above, a pure state of narcosis is slowly developed in about ninety minutes. It lasts approximately the same time, and is then replaced by the healthy normal condition.

Warm-blooded animals also are similarly affected by nitric acid. This is specially shown by means of hydroxylamine ($NH_2.OH$), which is converted into nitric acid in the animal system.[1]

Observations on sick and on healthy individuals confirm this.

M. Hay was able to afford more relief with sodium nitrite than with amyl nitrite to a man forty-two years old who was suffering from angina pectoris.[2] The prescription was half an ounce of sodium nitrite dissolved in 12 ounces of water, one to two teaspoonfuls to be taken as required, that is $2\frac{1}{2}$ to 5 grains for a dose. The patient usually took this dose four times in the twenty-four hours. Hay had tried the effect of this sodium nitrite upon himself and upon his friends. They took from 0·3 to 1·3 grammes (5 to 20 grains), but they apparently employed a solution which only contained 33 per cent. of the substance, and afterwards experienced "a feeling of fulness in the head and eyes accompanied by a throbbing sensation. There was also a slight, almost doubtful flushing of the countenance. The sense of fulness and throbbing continued for an hour or more; . . . . it was comparatively trifling, and caused no inconvenience." "The pulse became accelerated shortly after taking each dose, and most distinctly after the largest dose (20 grains)."

Fraser reports a case of bronchial asthma in which the patient was relieved a few minutes after taking 0·3 gramme (4·5 grains) of sodium nitrite. The feeling of relief increased, and was followed by sleep.[3] The sphygmographic

[1] C. Binz, "Toxikologische Studien über das Hydroxylamin und Natriumnitrit," 'Arch. f. path. Anat., u. s. w.,' 1888, Bd. cxviii, s. 1.

[2] M. Hay, 'Practitioner,' London, 1883, vol. xxx, p. 179; S. Ringer and W. Murrell, 'Lancet,' 1883, vol. ii, pp. 766—880.

[3] Thomas R. Fraser, "The Dyspnœa of Asthma and Bronchitis; its Causation and the Influence of Nitrites upon it," 'Trans. Edinburgh Med.-Chirurg. Soc.,' 1888, vol. vi (printed separately).

tracings which were taken both before and after the administration of the dose are of the same character as those produced by amyl nitrite (see p. 155). Similar cases have been observed in the Poliklinik of Professor J. Meyer[1] at Berlin. When the drug has been carelessly administered failure and even dangerous symptoms of poisoning have been the result.[2] This is not surprising if we bear in mind the effects produced upon animals, and the chemical properties of the remedy.

Sodium nitrite is sold in the form of small white rods which are deliquescent. It usually acts as a basic salt, owing to the presence of the carbonate or oxyhydrate. Even carbonic acid decomposes it in the presence of reducing substances. Nitrous acid is set free, but it is immediately decomposed into water, nitric acid, and nitrous oxide according to this formula :

$$3HNO_2 = H_2O + HNO_3 + 2NO.$$

As is well known, nitrous oxide has a very deleterious action upon living matter, consequently the amount which may possibly be developed within the human body must under no circumstances be allowed to exceed a very small quantity.

Another preparation allied to sodium nitrite—NITRO-GLYCERINE—has recently been introduced into therapeutics. This is produced when nitric acid and concentrated sulphuric acid act upon glycerine ; but the latter acid merely acts by absorbing the water which is given off, thus :

$$C_3H_5(OH)_3 + 6HNO_3 = 3H_2O + C_3H_5(NO_3)_3.$$

Nitro-glycerine is a nitrate, not a nitrite, though it is changed into a nitrite in the body, a change which also occurs if it is digested with the blood out of the body.[3]

[1] P. Fuchs, 'Ueber die therapeutische Wirksamkeit des Natriumnitrit,' Doctordiss., Berlin, 1884.

[2] Collischorm (two cases), 'Deutsche med. Wochenschr.,' 1889, s. 1844.

[3] M. Hay, "The Chemical Nature and Physiological Action of Nitroglycerine," 'Practitioner,' London, 1883, vol. xxx, p. 422 ; also ibid., p. 321 ; Rossbach, "Wirkung des Nitroglycerins auf die Schrumpfniere," 'Berl. klin. Wochenschr.,' 1885, s. 33 ; Fraser, loc. cit., 1888, Observations 6, 7, 9, and 14 ; W. Murrell, 'Therap. Monatshefte,' 1890, s. 532 ; Lilienfeld, 'Ber'. klin. Wochenschr.,' 1890, No. 44, s. 1027.

Korcynski, in Cracow, has published reports of experiments[1] with nitro-glycerine upon healthy people and upon thirty-five patients, in doses (taken internally) of 1—6, or at most 10—15 drops of an alcoholic solution of a chemically pure specimen. These experiments show that this drug corresponds to amyl nitrite, both with regard to its physiological action and also its therapeutic uses, in such cases as asthma with emphysema, angina pectoris, palpitations, and chorea. Other authors have furnished similar reports. Nitro-glycerine has this advantage over amyl nitrite, that its alleviating effect is more prolonged. On the other hand, according to these reports, when given in therapeutic doses its use is accompanied by headaches which, though unpleasant, are of a transitory nature. In a few days the patient becomes used to the drug, and not only does he cease to experience any inconvenience from its use, but even imagines that he is cured.

Nitro-glycerine is an oily liquid, insoluble in water; it cannot be prescribed alone on account of its explosive character. The only practical way of prescribing it is in small tabloids which are prepared with chocolate and gum-arabic. These may be bought containing either 0·0005 or 0·001 ($\frac{1}{1300}$ or $\frac{1}{650}$ of a grain) of the drug.[2] Ten to fifteen tabloids may be taken during the day.

The similarity of the essential action of these three preparations shows clearly that in amyl nitrite it is not the amyl, but the NITROUS ACID which is the active agent. This is especially plain in the case of sodium nitrite, for the sodium has no pharmacological action in the body, and certainly not the one we are discussing.

Sodium nitrite is not suitable for practical purposes, as it readily decomposes in the stomach, and this we have no means of preventing. It will be well to regard it as a substance which serves simply to illustrate and explain the general action of the nitrites.

[1] Korcynski, 'Wiener med. Wochenschr.,' 1882, s. 154.

[2] In England tabellæ are used containing $\frac{1}{100}$ of a grain (transl.).

IX.

Iodine—Formerly used in medicine as Spongia Usta—*Introduced into medicine in* 1820—*Its caustic action, both externally and internally—Experiments with it—Mode of administration—Effect of painting it upon the skin—Iodoform—Its chemical action and origin—Introduction into medicine—Surgical dressings—Liberation of free iodine from it—Poisoning by iodoform when used externally—Demonstrations on animals—Iodide found in the urine after using iodoform—Potassium iodide—Its decomposition by protoplasm and carbonic acid—Use in cases of metallic poisoning—The consequences of its prolonged use—How eliminated—Its absorption by the skin—Sodium iodide.*

We have now come to an important group, which has many points in common with the drugs previously mentioned, although it differs largely from them both in regard to its chemical origin and pharmaco-dynamic action; I refer to the iodine group.

Iodine in the free state is a dry, greyish-black substance consisting of rhombic laminar crystals with a peculiar odour, which when heated yield a violet-coloured vapour; it strikes a deep blue colour with solution of starch, is soluble in 5000 parts of water and in 10 parts of alcohol; the latter solution has a brownish colour. It readily dissolves in ether, and in a solution of potassium iodide, forming brown solutions, and in chloroform, with which it forms a violet-coloured solution.

M. Courtois, in 1811, was the first to prepare iodine from the ashes of burnt seaweed. Iodine is found in sea water in very small quantities (about 1 in 300,000), but seaweed takes it up to such an extent that the ashes of some species of this plant yield as much as 4·5 per cent. of free iodine.

For a long time burnt seaweed and sponges, as *Æthiops vegetabilis*, *Spongia usta*, &c., were used for swollen glands without their really active constituent being known. After the discovery of the new element, Straub, of Hofwil, near Berne, in 1819 suggested that it was the chief ingredient of these remedies, and Fyfe in the same year discovered it in the ashes of burnt sponges. Coindet, of Geneva, in 1820 published his treatise 'Découverte d'un nouveau remède (Iode) contre le Goitre.' Since that time iodine has not only been recognised as a medicine even during most sceptical periods, but has extended its field of action every year.

If metallic iodine is brought in contact with the skin, it at once produces a brown discoloration, which soon disappears if the duration of contact is short; it acts as a caustic if allowed to remain in contact with the skin for any length of time. This caustic action takes place very readily on mucous membranes. In one case a man swallowed 30 grms. of tincture of iodine,[1] with the result that inflammation of the œsophagus, stomach, and small intestine came on almost immediately, together with violent pain, vomiting, and diarrhœa. In a short time the man collapsed, and died thirty-three hours after taking the tincture.

Nevertheless it is a fact that mucous membranes are not so much affected by iodine as by other caustics, and this fact has caused Magendie and others to imagine that little regard should be paid to its caustic action.[2] But this is a mistake, and one which has doubtless proved serious to a great number of patients. A case in point has been related by Rose.[3]

The patient was a young girl with an ovarian cyst. The cyst was punctured and injected with 150 grms. of tincture of iodine, diluted with 150 grms. of water to which 3·6 grms. of potassium iodide had been added. The whole of this solution was allowed to remain for about seven minutes in the cyst, and was then slowly let out, the latter part of

[1] F. Herrmann, 'Petersburger med. Wochenschr.,' 1868, Bd. xv, s. 336.

[2] See Bernatzik, 'Die gebräuchlichsten Iodpräparate,' Wien, 1853, s. 6.

[3] E. Rose, 'Arch. f. pathol. Anat.,' 1866, Bd. xxxv, s. 12.

the operation lasting for ten minutes. Six hours afterwards the patient was seized with vomiting and violent thirst, her pulse being hardly perceptible. On the next day the vomiting recurred with pain in the abdomen, and the patient became very drowsy and delirious. During the following days albumen appeared in the urine, the pain in the region of the stomach increased, the temperature gradually fell, the vomiting and drowsy condition continued, whilst the urine became scanty, and on the tenth day death quietly took place.

These statements of Rose as to the results which followed the absorption of iodine by the cyst wall are confirmed by what I have myself seen after its absorption from the subcutaneous cellular tissue.[1]

A rabbit weighing 200 grms. was *subcutaneously* injected at considerable intervals during the afternoon with an aqueous solution of 0·045 grm. (0·675 grain) of iodine, to which a little sodium iodide had been added, and 0·02 grm. ($\frac{1}{3}$ of a grain) in a single dose next morning. It died two hours afterwards. On *post-mortem* examination numerous punctiform ecchymoses were found in the stomach, the surface of this being uniformly red and its mucous membrane greatly swollen.

A second rabbit of the same age, when poisoned in the same manner with iodine, gave nearly the same results. In the case of a third and older animal, which had been injected subcutaneously twice in two hours with 0·075 grm. of iodine two large ecchymosed strips were found in the fundus of the stomach, and a large number, of a punctiform character, towards its anterior and upper surfaces. The surrounding surface was very red and the mucous membrane highly congested. Externally the stomach was unaffected, but the mesentery was very vascular.[2]

If free iodine dissolved in a weak aqueous solution of sodium iodide be injected directly into a blood-vessel, the pleura becomes highly inflamed and hæmorrhagic effusion takes place into both its cavities, and there is considerable

[1] C. Binz, "Toxicologisches über Iodpräparate," 'Arch. f. exper. Path. u. Pharmakologie,' 1880, Bd. xiii, s. 117.

[2] R. Böhm, ibid., 1876, Bd. vi, s. 342.

œdema of the lower lobes of both lungs. The kidneys are very vascular, and show hæmorrhagic extravasations confined almost exclusively in the tubules.

This action of iodine upon the mucous membrane of the stomach when absorbed from some peripheral part, as in the cases reported by Rose and myself, may be explained on chemical grounds as follows.

I have here some clear blood-serum which is alkaline; on adding to it a few drops of a very dilute solution of iodine and potassium iodide in water the colour of the iodine goes, and the fluid becomes colourless and remains alkaline. If, however, I previously make the serum neutral, the first few drops of iodine are sufficient to render it acid.

If now I were to separate, by coagulation or by dialysis, the serum-albumin from the water and salts, I could easily show that the iodine is combined with the alkali in two ways, —as an iodide and as an iodate, *i. e.* as NaI and $NaIO_3$. The molecular proportions are shown by quantitative analysis to be five to one. If we remember that sodium carbonate and bicarbonate are the principal alkaline salts of blood-serum we see that this reaction must take place.

$$6NaHCO_3 + 3I_2 = 6CO_2 + 3H_2O + 5NaI + NaIO_3.$$

That the iodide is not—as has been supposed—the only salt present in such a solution is proved by the following experiments. If I add pure diluted hydrochloric acid to this solution of pure sodium iodide in water until it is strongly acid, the solution remains colourless. If I make the same experiment with serum, it turns yellow at once from the presence of free iodine, thus: $5NaI + NaIO_3 + 6HCl = 6NaCl + 5HI + HIO_3$; but as double decomposition always takes place when hydriodic and iodic acids are brought together, we have $5HI + HIO_3 = 3H_2O + 3I_2$.

When iodine is absorbed either by the lymphatics of an ovarian cyst or from the subcutaneous connective tissue, it always meets with an alkaline carbonate, and so the iodide and iodate are formed. These two bodies circulating in the blood necessarily yield free iodine in tissues which have an acid reaction as readily as they do here in the test-tube, and

this liberated iodine then immediately acts as a caustic upon the tissues.

On account of this caustic action free iodine is rarely used internally, but it has been recommended as of service in cases of obstinate vomiting which have a nervous origin, though we are not informed what the special indications for its use are, nor in what way it effects a cure. In these cases tincture of iodine is given, which contains one part of iodine in ten of alcohol.[1] One to two drops of the German tincture may be given as a single dose, and this may be very carefully increased; 0·2 gramme of the tincture, which is equivalent to about four drops, is the maximum dose allowed by the Pharmacopœia, and this corresponds to about 0·02 gramme ($\frac{3}{10}$ of a grain) of iodine. The maximum dose of free iodine is stated to be 0·02 gramme; it may be prescribed in doses from 0·005 gramme upwards. Free iodine is, however, not easily dispensed, and consequently is seldom used.

The ANTIZYMOTIC action of iodine has also been utilised internally in typhoid fever and in anthrax, but the experiments with it in these diseases have now only a theoretical interest.[2]

In cases of POISONING by tincture of iodine we must first neutralise any free iodine still in the stomach by administering some non-caustic alkali in excess, and the contents of the stomach must then be washed out. White of egg is usually available, and it has an alkaline reaction; milk will also serve the purpose. Starch and substances containing starch have been recommended, but they cannot be depended on, for the compound formed by the action of iodine upon starch readily gives up its iodine to albuminous substances, and therefore would be decomposed by the walls of the stomach.

As in other cases of corrosive poisoning, it is most important that the pain in the intestines should be relieved. If pain continues for some days, this is quite sufficient to lower the action of the heart and exhaust the nervous centres.

[1] 1 in 40—'Ph. Brit.'

[2] v. Willebrand, 'Arch. f. pathol. Anat.,' 1865, Bd. xxxiii, s. 517; Liebermeister, 'Arch. f. klin. Med.,' 1868, Bd. iv, s. 421; C. Davaine, ref. 'Centralblatt f. d. med. Wiss.,' 1881, s. 33.

Tincture of iodine is very frequently used EXTERNALLY. It is painted upon the skin, and the application is usually repeated until the part becomes tender and painful, and the rete mucosum is laid bare. In this way the absorption of exudations and swellings, which are not too deeply seated, is aimed at, and in a considerable number of cases is successfully accomplished. Iodine in all forms, and especially when applied in this way, is regarded as an "absorbent" remedy.

We know very little concerning the nature of this absorbent action. Derivative action, revulsion, counter-irritation, increased vascular activity, are merely words, and convey no clear idea. The action is only comprehensible from two points of view.

Iodine is very destructive to most living cells, so that if it is applied—in the form of the tincture or liniment—until it reaches the morbid cell-growth, this, if not of a malignant nature, has its growth checked by the protoplasmic poison and gradually disappears. It is then said that iodine has promoted the absorption of the swelling through the vascular system, though we are unacquainted with any facts which can support such an idea.

This first explanation can only be accepted if iodine is absorbed by the skin, passes into the system, and reappears in the urine. This has been affirmed[1] and contradicted[2] from the result of experiments which have been made.

Demarquay found that when large portions of the skin of patients in hospital wards were painted with tincture of iodine, not only did the urine of the patients so treated contain iodine, but it also appeared in the urine of the other patients, as well as in that of the physician who conducted the experiment. Röhrig fixed his forefinger in a bottle containing tincture of iodine, in such a way as to prevent the ingress or egress of air, but not to interfere with the circulation. For fifteen minutes the tincture was brought, by shaking the bottle, in full contact with the skin. As he drew his finger out suitable precautions were taken to prevent the vapour of the iodine from reaching his lungs; nevertheless

[1] Röhrig, 'Die Physiologie der Haut,' Berlin, 1876, s. 102.

[2] R. Fleischer, 'Untersuch. über d. Respirationsvermögen der Haut,' Erlangen, 1877, s. 64.

three times in succession he readily found iodine in the urine passed an hour afterwards.

The second explanation of this action of iodine is that the drug acts as an external irritant and sets up acute ERYSIPELAS. When this condition subsides or diminishes the surrounding cells are absorbed.

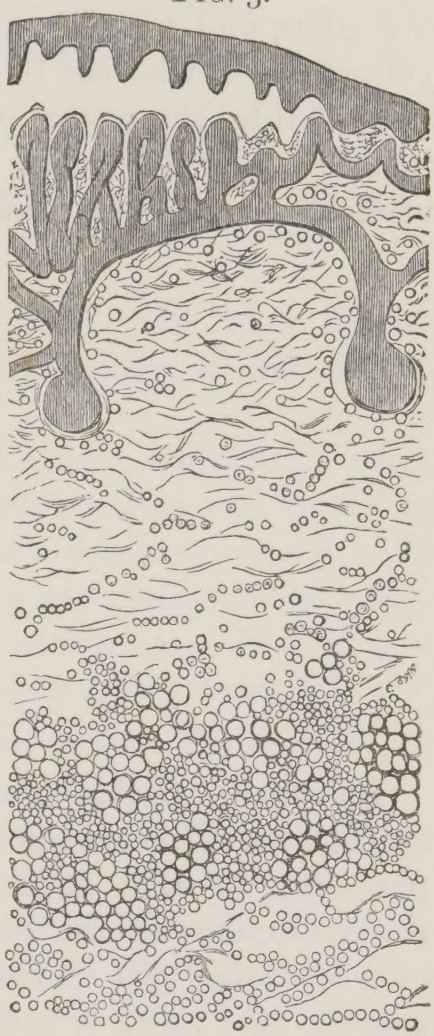
Schede[1] painted the skin of some rabbits with tincture of iodine. A few hours afterwards there was considerable exudation and accumulation of lymphoid cells, first in the subcutaneous cellular tissue, then in the corium, in the cellular tissue between the muscles, and in the periosteum. Inflammation of the medulla of the bones with rarefaction and absorption of the epiphysial cartilages followed. The lymphoid cells, which were present in large numbers—mostly round the blood-vessels—were undoubtedly wandering white blood-corpuscles. After the skin had been painted with iodine for about a week certain changes began to occur. Small droplets of fat, which were produced by the fatty degeneration of these migrating cells, made their appearance. The adjacent cellular tissue was involved in the change, and after undergoing fatty degeneration became disintegrated and absorbed. Some of these changes are depicted on next page.[2] The epidermis is separated from the rete Malpighii, and the wandering white corpuscles are present in large quantities in the serous fluid, around the blood-vessels, and in the cutaneous tissue, but most abundantly among the fat cells of the subcutaneous tissue. The skin is considerably swollen, so that the emigration of corpuscles is facilitated, whilst the blood-vessels are considerably dilated. This infiltration of cellular elements becomes greater in the deeper layers of the skin. R. Volkmann has shown this to be the case also in the healthy human skin. He painted the healthy skin of a patient's limb, which was to be amputated

[1] Schede, "Ueber die feineren Vorgänge nach der Anwendung starker Hautreize, besonders der Jodtinctur." Ref. 'Centralbl. f. d. med. Wiss.,' 1872, s. 857; E. Coen, "Ueber die Veränderungen der Haut nach Einwirkung von Jodtinctur," in Ziegler's und Nauwerk's 'Beiträgen,' Jena, 1888, Bd. ii, s. 29.

[2] After Volkmann's Tafel I in the 'Handb. d. allgem. u. spec. Chirurgie,' Erlangen, 1869, Bd. i, Abt. 2.

on the following day, with tincture of iodine. On examining this portion of the skin microscopically, "enormous exudation of white corpuscles, such as is found in diffuse abscesses,"[1] was observed.

Fig. 5.



Erysipelas would thus appear to be artificially induced by painting with iodine, for we know that in erysipelas the above are the essential anatomical processes,[2] however diverse the causes and the consequent character of the erysipelatous inflammation may be. Further, it has been repeatedly proved by clinical observation that erysipelas promotes the absorption of tumours.

It is a point of practical importance—to which attention has often been called—that wide-spread inflammation, both externally and internally, may be set up by painting the skin with iodine, especially in children. Skin eruptions in parts of the body at some distance from the irritated spot, albuminous urine, and affections of the nervous system are some of the results mentioned.[3] In adults, violent irritation of the kidneys has followed the external application of tincture of iodine. These results are, however, exceptional; still, as they do occur, it is well to bear them in mind.

For surgical purposes tincture of iodine is not generally used, on account of the pain caused by the alcohol; whilst if it is diluted with water the iodine is precipitated. A solu-

[1] R. Volkmann, 'Verhandl. des 1. Chirurgen-Congresses,' Berlin, 1872, s. 20.

[2] Volkmann und Steudener, 'Centralbl. f. d. med. W.,' 1868, s. 561.

[3] Zesas, 'Wiener med. Wochenschr.,' 1882, s. 530; Lorenz 'Deutsche med. Wochenschr.,' 1884, s. 733. "Acute Vergiftung bis zur Bewusstlosigkeit nach dreimaliger handtellergrosser Aufpinselung auf den Arm eines erwachsenen Mannes."

tion of iodine in water containing a little potassium iodide is therefore employed instead. Iodine is soluble in an aqueous solution of the iodides. If I put some iodine into this glass and then shake it, the water has only a slightly yellow tinge, whereas if I add but a single crystal of potassium iodide, the water becomes opaque and brown, as the iodine is now dissolved. In this form iodine may also be used for purposes of disinfection.

Iodoform—CHI_3—must be considered next to free iodine among the Pharmacopœial preparations, as it contains 96·7 per cent. of that substance. $C = 12$, $H = 1$, $3 \times I = 381$; the molecular weight of iodoform is 394, and as this molecule contains 381 parts of iodine, 100 parts of iodoform contain 96·7 parts of iodine.

It consists of small, shining, hexagonal, crystalline scales, somewhat greasy to the touch; they have a lemon-yellow colour, and a persistent and somewhat saffron-like odour. Iodoform melts at about 120° C. (248° F.); is volatilised in steam; is almost insoluble in water (1 in 5000 parts); is soluble in 50 parts of alcohol, in 5·2 of ether, and about 2·5 parts are soluble in 100 parts of olive oil.[1] When heated it gives off brown and violet vapours, and is decomposed into iodine, hydriodic acid, and carbon.

Iodoform may be prepared by acting upon various organic compounds with iodine and an alkali; alcohol is the most convenient of these substances.

I have in this test-tube some very dilute alcohol, to which

[1] F. Klingemann, 'Centralbl. f. Chir.,' 1890, No. 32.

I add a few drops of a solution of iodine and potassium iodide, and then sufficient caustic soda to remove the yellow colour. I now heat it to about 60° C. (140° F.). On cooling, the solution, which was previously quite clear, becomes opaque and yellow, and if we examine a drop under the microscope we see numerous small hexagonal scales or stars of iodoform. The mode of formation is as follows :

$$4I_2 + C_2H_5.HO + 6NaHO = 5H_2O + NaCHO_2 + 5NaI + CHI_3.$$

Sérullas discovered iodoform in 1822. In 1834 Dumas recognised that it was similar in composition to chloroform, and named it accordingly.

Bouchardat recommended its use as a remedy in 1840. From the fact that it contains so much iodine and causes so little irritation when employed externally, it appeared to be a very suitable remedy to administer internally in the treatment of scrofula, goitre, and amenorrhœa. Bouchardat gave it with good results, beginning with doses of 0·05 gramme ($\frac{3}{4}$ of a grain), and gradually increasing it until the patient took 0·6 gramme (9 grains) a day.

From that time iodoform was used in France and other countries, though it was hardly noticed in Germany. In 1875 a memoir was published recommending it as a purifying and slightly stimulating agent, and as having possibly a specific curative action.[1] Its value in surgical dressings is much discussed at the present time.

It is held in considerable repute by surgeons as an antiseptic. It is said to check suppuration, to promote the healing of wounds, and occasionally to lessen the pain of ulcerated surfaces and recent wounds. How is it able to produce these various effects ?

The old saying—"Corpora non agunt nisi fluida"—is not out of place in this connection. As yet, no medium with the exception of fat has been discovered in the normal tissue which can dissolve iodoform to any appreciable extent. Blood-serum dissolves iodoform in about the same proportion as water does (1 in 5000—A. Zeller). Fat is usually present

[1] A. Lazansky, 'Vierteljahrschr. f. Dermatol. u. Syphilis,' 1875, s. 275.

on the surface of wounds and ulcers, and will dissolve finely powdered iodoform, which is then decomposed and free iodine is liberated.

I have in this tube some ether which has been exposed for a time to the action of light, and consequently contains a small quantity of hydrogen peroxide. If a little iodoform is added it is instantly dissolved, and gives the solution a light yellow colour, which however, quickly becomes brown when the solution is shaken for a few minutes.

The fact that iodine is liberated by the action of fat upon iodoform may easily be proved by another experiment. If I suspend a strip of paper moistened with starch in a flask containing a solution of iodoform in oil of sweet almonds, it will be coloured blue in about a quarter of an hour.[1]

Iodine can only be set free from iodoform, when in solution, in the presence of oxygen and light.[2] Consequently in wounds which are closed, and in ulcers which are bandaged, one of these conditions for its liberation is absent, though the other is supplied by the oxygen of the oxyhæmoglobin. It can be proved, however, experimentally that iodoform which has been dissolved in the fat of living tissues is also decomposed without the presence of light. The action of the light, therefore, is replaced by that of the cells.

Though undissolved iodoform has no effect upon septic processes, we know that free iodine is an active antiseptic and antiparasitic. When this element is slowly given off by iodoform its presence prevents a septic condition in the wound,[3] and purifies it from any infection which may be present;[4] it also prevents any active emigration of the

[1] C. Binz u. Möller, "Ueber Jodoform und über Jodsäure," 'Arch. f. exper. Path. und. Pharmak.,' 1878, Bd. viii, s. 309.

[2] Behring, 'Deutsche med. Wochenschr.,' 1882, s. 278.

[3] v. Mosetig-Moorhof, 'Wiener med. Wochenschr.,' 1880, No. 43, &c.

[4] J. Mikulicz, 'Arch. f. Chirurgie,' 1881, Bd. xxvii, ss. 1—45. For exhaustive references to the experiments and literature of the subject see A. Neisser, "Zur Kenntniss der antibakteriellen Wirkung des Jodoforms," 'Arch. f. path. Anat.,' 1887, Bd. cx, s. 281. For a less detailed account see among others A. Kunz, in Ziegler's and Nauwerk's

white blood-corpuscles by paralysing their protoplasm,[1] and allows the free growth of granulations by preventing decomposition. It further lessens sensation in the nerve-endings which are exposed, partly in the same way but partly by direct paralysis of the axis-cylinders.

We do not know what becomes of the carbon and hydrogen atoms in this decomposition. The fact that oxygen is required for the reaction makes it probable that the 3·3 per cent. of the CH set free from the CHI_3 is oxidised in this manner:

$$2CH + 5O = 2CO_2 + H_2O.$$

Högyes and others have supposed that the iodine which is set free from the iodoform first of all combines with the fluids of the body as an albuminate, and that the metalloid is then liberated from this compound.[2] This may be so, but it is an unimportant link in the chain. Högyes showed that such an albuminate of iodine gives off all its iodine in the dialyser, after a few minutes, in the form of iodide and iodate; and further that when it is subcutaneously injected in animals it causes the same poisonous symptoms as iodine.

Hæmoglobin, gelatine, and uric acid, combine with free iodine; and the disappearance of small quantities of iodine in the urine is due to this acid. Urea does not combine with iodine. It is not yet clear under what conditions these compounds are formed, nor whether they are of any consequence in the animal economy.

Fat, however, is not the only means by which iodoform is decomposed; the ptomaïnes, which are so often found in a

'Beiträgen,' Jena, 1888, Bd. ii, s. 175. M. Freyer sums up the whole question in the 'Therap. Monatshefte,' 1888, s. 287. P. Bruns und C. Nauwerck, "Ueber die antituberculöse Wirkung des Jodoforms, klinische und histologische Untersuchungen," in the first series of 'Beiträge zur klinischen Chirurgie,' 1887, Bd. iii, s. 133. P. Bruns, 'Ueber die Behandlung tuberkulöser Abscesseund Gelenkerkrankungen mit Jodoforminjectionen,' Daselbst, 1890, Bd. vi, s. 639. Wendelstadt, 'Centralbl. f. Chir.,' 1889, No. 38.

[1] C. Binz, "Ueber das Verhalten der Auswanderung farbloser Blutzellen zum Jodoform," 'Arch. f. path. Anat.,' 1882, Bd. lxxxix, s. 389; R. Heinz, 'Berl. klin. Wochenschr.,' 1890, s. 1186.

[2] Högyes, 'Arch. f. exper. Path. und Pharmakol.,' 1879, Bd. x, s. 228.

wound, also have this action. This has been proved, at any rate as far as pentamethylendiamine (Brieger's cadaverine) is concerned. The two substances react with each other in such a way that they undergo chemical changes, and cadaverine loses its power of setting up suppuration. If pure cadaverine is mixed with iodoform, the latter is dissolved and free iodine is given off even at cold temperatures, though more freely when heated. Moreover iodoform is easily decomposed by nascent hydrogen, and by bacteria which have a reducing action. If it is added to a culture of tubercle bacilli on blood-serum which is kept in an incubator, it prevents any growth of the bacilli; but how it does so is not known.[1]

In the decomposition of iodoform by nascent hydrogen, Behring has noticed the appearance of acetylene, C_2H_2. This would therefore also take place in a mixture of water (from which air is excluded) and finely divided iodoform, according to the formula—

$$2CHI_3 + 3H_2 = 6HI + C_2H_2.$$

Nascent hydriodic acid is formed in any case—a fact recently discovered by Klingemann in my laboratory.

At first surgeons paid little attention to what pharmacological research had discovered with regard to the dangerous properties of iodoform, and consequently in the treatment of wounds as much as possible of the drug was put into them in order to keep them aseptic. Very dangerous and even fatal results followed, and this led to a strong reaction against its employment as a surgical dressing, notwithstanding the excellent results which had so often previously attended its use.[2] Insomnia, depression, irritability, loss of memory, hallucinations, loss of appetite, vomiting, bloody urine, cutaneous eruptions, violent delirium, and even death following upon œdema of the lungs and direct paralysis of the heart, were frequently reported[3] as being produced by it;

[1] Behring, 'Deutsche med. Wochenschr.,' 1887, No. 20, and 1888, No. 32.

[2] R. Falkson, 'Arch. d. klin. Chirurgie,' 1882, Bd. xxviii, s. 112.

[3] König, 'Centralbl. f. Chirurgie,' 1882, Nos. 7 und 8.

and after death, fatty degeneration, especially of the liver, was observed as one of the pathological results.

The pharmacological experiments conducted by myself, by Högyes, and by Behring, have furnished an explanation of its *modus operandi*.[1]

If iodoform is once dissolved in the fat or ptomaïnes present in wounds or ulcers, then iodine is set free. The vapour of the metalloid then passes into the body fluids, and goes through those changes which I have described as taking place when iodine dissolved in an aqueous solution of potassium iodide is mixed with serum. It is resolved into five molecules of iodide and one of iodate, from which, in those tissues having an acid reaction, iodine is again set free, and acts on the tissue in which it is liberated. The iodate is continuously reduced until, no fresh iodine being introduced, it is exhausted, and the iodide eliminated in the urine.

The CEREBRAL CORTEX is one of the tissues which has an acid reaction.[2] Its very sensitive cells, continuously influenced by the iodine which is liberated in the tissue, must have their specific action essentially modified. The effect of this action is to cause those disturbances of the system, formerly observed in surgical practice, to which I have above referred.

This action on the cells of the cerebral cortex, which is partly stimulating and partly depressing, shows itself only in the morbid mental conditions produced by it; in another organ, however, which has an acid reaction—THE MUCOUS MEMBRANE OF THE STOMACH—the effect on the part can be directly demonstrated.

You see spread out on this plate the internal surface of the stomachs of two very young unweaned rabbits; to the one was given a few hours back two SUBCUTANEOUS injections of iodoform dissolved in oil of sweet almonds; nothing was done to the other. Both animals were killed by cutting their throats.

[1] C. Binz, 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. viii, s. 309, and 1880, Bd. xiii, s. 113; Högyes, ibid., 1879, Bd. x, s. 228; Behring, loc. cit., 1882, Nos. 11, 20, 21, 23, and 24.

[2] Gscheidlen, 'Arch. f. d. ges. Physiol.,' Bd. viii, s. 175; Pflüger, ibid., Bd. x, s. 312; Edinger, ibid., Bd. xxix, s. 251; Ehrlich, 'D. med. Wochenschr.,' 1886, s. 52. The last author only partly allows that the cerebral cortex has an acid reaction.

The mucous membrane of the latter is pale and wrinkled; that of the former is red, swollen, and when drawn out, remains flaccid. This difference is very marked; we have in the one case a normal, in the other an inflamed mucous membrane.

The stupor which is caused by iodoform, can be produced in dogs or cats; it has much the same character whether we give the preparation by the stomach or, dissolved in oil, by the skin. I have here a young dog of about 1500 grms. weight to which about 2 grms. (30 grains) of iodoform in a little oil was subcutaneously administered an hour ago. It is sluggish, drowsy and can hardly stand. The animal will waste rapidly during the next few weeks, but it need not necessarily die. No abscesses will be developed at any of the various punctures.

In animals which have succumbed to iodoform poisoning, fatty degeneration of the hepatic lobules, especially in the outer third, and also of the cardiac muscle and renal tubules is found after death. This has also been found in the human subject, but many cases die from paralysis in whom no fatty degeneration of the organs can be found after death, but instead, œdema and inflammation of the pia mater. The temperature falls during the poisoning process.

After the use of iodoform, externally or internally, iodides and iodates are found in the urine. I have already explained why iodic acid may be present, although, from the small quantity found, it must in most cases be quickly reduced to hydriodic acid. Lustgarten, adopting a process by which the presence of 2 to 3 mg. ($\frac{1}{30}$ to $\frac{1}{20}$ grain) of iodoform in a comparatively large quantity of urine could be demonstrated, found no trace of iodoform in the urine of people treated with this substance, though many of them had marked symptoms of poisoning. Nor did he find it in the blood of warm-blooded animals which had been poisoned, though not fatally, by the introduction of iodoform into the abdominal cavity.[1] Surgeons assert that the symptoms of iodoform poisoning may continue even after iodine has ceased to be present in the urine. This may be due to two reasons: first, that iodoform, or

[1] Lustgarten, 'Sitzungsber. der Akad. der Wissensch.,' Wien, 1882, s. 85; Harnack, 'Berl. klin. Wochenschr.,' 1882, No. 20.

rather the iodine which it gives off, has produced such changes in the cells of the brain that they only gradually return to a normal condition; and secondly, that iodine is present in the organism and in the urine, not as potassium iodide, but as an organic compound which is not detected by the usual tests—mucilage of starch, acidulation, oxidation, or a mixture of mucilage of starch and chlorine.[1] Further, it may be also due to the fact that the tests for iodine even in the form of potassium or sodium iodide have not been properly applied; this has been repeatedly shown in discussions as to the behaviour of iodoform in the system.

Iodoform has been given INTERNALLY for a long time back, chiefly in North America, especially in cases of obstinate cardialgia, trigeminal neuralgia, sciatica, malarial diseases, syphilis, and so on.[2] It became more generally known as a remedy in Germany in 1878, when Moleschott used it for internal complaints.[3] He gave iodoform internally in doses up to 0·4 grm. (6 grains) a day, and he reported good results with it in cases of leuchæmia, serous effusions, swelling of the lymphatic glands, and even in tuberculous meningitis of children.[4] He also prescribed a solution of iodoform in flexible collodion, to be painted twice daily over large areas of skin. In order to disguise the odour, which is most unpleasant to some people, he added to it cumarine ($C_9H_8O_2$), the odoriferous principle of the Tonka bean, *Dipterix odorata*, and of *Asperula odorata* and several other plants. The following is the formula :—Iodoformi 1 grm. (15 grains) ; Extract. Glycyrrh. Liquid. 1 gramme ; Cumarini 0·1 grm. M. ft. pil. xx. To be coated with gum arabic.

A portion of the albumen in the food is converted during the process of decomposition in the intestines into certain aromatic bodies (phenol, indol, skatol, cresol, &c.) ; these are

[1] T. Gründler, ' Die Form of Ausscheidung der Jodes im menschlichen Harn nach äusserlicher Anwendung des Jodoforms,' Halle, 1883, Doctordissertation.

[2] Ref. ' Centralb. f. d. med. Wissensch.,' 1870, s. 544.

[3] J. Moleschott, " Ueber die Heilwirkungen des Jodoforms," ' Wiener med. Wochenschrift,' 1878, Nos. 24—26; 1882, Nos. 17—19.

[4] The convulsions in this disease are seemingly arrested by it. See Windelschmidt, ' Allgem. med. Centralztg.,' 1881, s. 542.

absorbed and combine with sulphuric acid in the organism to form phenol-sulphonic acid, indol-sulphonic acid, &c., the salts of which are excreted in the urine. The amount of these salts present is a measure of the amount of putrefactive decomposition going on in the intestines. When iodoform was given internally to a dog it greatly diminished this putrefactive change.[1]

Sigmund has also recommended iodoform in syphilis, and the good results obtained by him have been often repeated. Thormann injected it in such cases subcutaneously, using one part of iodoform to eighteen of almond oil, and making several injections daily in different parts of the body. The above solution does not cause cutaneous suppuration, but the syringe must be of opaque glass, for otherwise free iodine would be quickly liberated, and might set up inflammation at the point of injection.[2] It is evident that iodoform may also act as a poison, when given internally. It is dissolved in the fatty contents of the intestines, and perhaps also in other media, and goes through the same changes as in the case of external wounds. Two cases have been described,[3]—and there have been many others since—in one of which after 5 grammes (75 grains) had been taken in seven days, and in the other 42 grammes (630 grains) in eighty days, dangerous depression of the nervous system was set up, which persisted for several days after the drug had been discontinued.

Theoretical considerations led to the treatment of cases of iodoform poisoning by alkalies.[4] When either it or chloroform is taken, the acidity of the urine is increased, the excretion of alkalies being diminished;[5] and the more alkaline the system, the less readily is iodine liberated from

[1] Baumann und Morax, 'Zeitschr. f. physiol. Chemie,' 1886, Bd. x, s. 318.

[2] E. Thormann, 'Centralbl. f. d. med. Wissensch.,' 1881, s. 785; O. Kniffler, 'Jodoform zur inneren Anwendung,' Bonn, 1890, Doctor-dissertation. Unter Behring's Leitung. (Its administration, dissolved in oil, as an enema to tuberculous animals, and in one instance to a man.)

[3] F. Oberländer, 'D. Zeitschr. f. prakt. Med.,' 1878, No. 37.

[4] Behring, "Ueber Iodoformvergiftung und ihre Behandlung," 'Deutsche med. Wochenschr.,' 1884, No. 5.

[5] See Kniffler's 'Dissertation,' ss. 25 u. 26.

the iodides and iodates. It now appears to be established that by giving several doses of one gramme (15 grains) of sodium bicarbonate, we can alleviate the symptoms and lessen the effects of iodoform poisoning.

The smell of iodoform is very much disliked by many people, and consequently another organic compound of iodine is sometimes used, namely IODOL. This is prepared from iodine and pyrrol, the latter being one of the products of the dry distillation of nitrogenous compounds; its formula is $C_4H_4.NH$. Iodol is C_4I_4NH, or tetra-iodopyrrol. It is a light yellow, odourless powder, hardly soluble in water, readily in alcohol, and still more so in ether, and contains 88·97 per cent. of iodine; oil dissolves about 6 per cent. of it. When applied to animal tissues it is absorbed; at least, it acts as an antiseptic, and appears as a soluble compound of iodine in the urine.

Iodol was first described by the chemists Ciamician and Silber, in Rome, in January, 1885, and it was prescribed there by G. Mazzoni.[1] Since that time it has often been used instead of iodoform. It is not, however, innocuous, as was shown in a case where 5 grammes (75 grains) sprinkled over a wound caused restlessness and delirium, followed by insensibility.[2]

POTASSIUM IODIDE, KI, occurs in the form of colourless crystalline cubes, which are not deliquescent; it has a saline taste which is followed by a bitter one, is soluble in 0·75 part of water or twelve parts of alcohol. If a little chlorine is

[1] G. Mazzoni, 'Berl. klin. Wochenschr.,' 1885, s. 695, und 1886, s. 694.

[2] Ref. in 'Therap. Monatsheften,' 1887, p. 324.

added to its aqueous solution, iodine is set free, giving to the solution a yellow, and if chloroform is added, a violet colour; on adding tartaric acid to the solution of potassium iodide a crystalline deposit of potassium bitartrate is formed on standing, together with free hydriodic acid, thus:

$$KI + H_2.C_4H_4O_6 = KH.C_4H_4O_6 + HI.$$

Potassium iodide is prepared on a large scale—amongst other methods—by mixing iodine with a somewhat concentrated solution of caustic potash, and then gently heating until the iodine no longer discolours the solution:

$$6KOH + 3I_2 = 3H_2O + 5KI + KIO_3.$$

This is evaporated to dryness, and in order to reduce the potassium iodate which—as appears from the formula—is also formed, the residue is mixed with charcoal and fused in a red-hot iron crucible, when the following reaction takes place:

$$6C + KIO_3 = 6CO + KI.$$

In order to detect the presence of potassium iodate, which would impede the absorption of the potassium iodide in the stomach owing to liberation of free iodine by the hydrochloric acid of the gastric juice (see page 167), we add to a 5 per cent. solution of the salt some PURE dilute sulphuric acid and a little mucilage of starch. A blue coloration will only appear after a time, not immediately, for—

$$2KI + H_2SO_4 = K_2SO_4 + 2HI;$$

and if the salt is pure, only potassium sulphate and hydriodic acid are at first formed. The latter is not resolved into water and free iodine until it has been exposed to the air for some time. If, however, iodic acid is also present, free iodine is at once liberated and develops the blue colour.

Wallace of Dublin introduced potassium iodide as a medicine about 1830, prescribing it instead of iodine, which up to that time had been used in the treatment of syphilis. The preparation has since kept its place, and its use has extended. It is employed chiefly in the treatment of syphilitic, glandular and rheumatic swellings.

As potassium iodide possesses little affinity for albumen

and other constituents of the human body, it is difficult to explain how the beneficial effects which result from its use arise. I therefore sought for "some evidence that conditions might possibly occur in the body by which the iodine of this chemically inactive salt might at times be liberated,"[1] and found it by applying and utilising a fact noticed by Schönbein, viz. that certain parts of plants, when ground with water and acidulated, decompose potassium iodide almost immediately.

It was not known what the active agent in this decomposition was, but as the result of further experiments I showed[2] that it was the PROTOPLASM which was liberated from the cell-walls of the plant. This imparts activity to the oxygen of the air, and the same result occurs when very small quantities of nascent or active oxygen act upon an acidulated solution of potassium iodide. If we use carbonic acid as an acidifying agent, we have the same condition as exists in the human tissues. The simple experiment may be made as follows :

A fresh leaf of *Lactuca sativa*, which is very rich in protoplasm, is ground in a mortar together with a few cubic centimetres of water; a 1 per cent. solution of potassium iodide—or better, sodium iodide—is saturated with carbonic acid at a temperature of 15° C. (59° F.), a little mucilage of starch is added, and the mixture divided into two parts. I add to the one half some of the protoplasm and water, which has a neutral reaction; to the other, the same quantity of ordinary water. The latter remains undecomposed even when it has stood for a long time. In the former, as you see, the blue coloration begins to appear in a few minutes, indicating the liberation of free iodine, and is then rapidly and fully developed.

Just as carbonic acid by itself cannot liberate the iodine, so neither can the protoplasm do so unless the acid is also present. Naturally this does not hold good for an indefinite time, as every solution of potassium iodide will gradually

[1] C. Binz, "Die Zerlegung des Jodkaliums im Organismus," 'Arch. f. path. Anat.,' 1875, Bd. lxii, s. 124; 'Arch. f. exper. Path. u. Pharmak.,' 1894, Bd. xxxiv, s. 185.

[2] C. Binz, 'Arch. f. path. Anat.,' 1869, Bd. xlvi, s. 145.

decompose under the influence of light, air, and organic matter.

If I HEAT the vegetable solution, the whole reaction is prevented, thus showing that it is due to LIVING protoplasm. Again, it is not here a question of a liberated oxidising acid, as is possibly the case with human saliva, for though this also immediately turns an acidified potassium iodide paste, blue, it does not lose this property when boiled. As is well known, this is supposed to be due to the presence of salts of nitrous acid; the acid is first liberated, then combines with the potassium and sets the iodine free.

The chemical changes which take place in our experiment with carbonic acid and protoplasm are given by the following formula:

$$KI + H_2O + CO_2 = KHCO_3 + HI,$$
$$2HI + O = H_2O + I_2,$$

that is to say, carbonic acid first acts upon potassium iodide so that potassium bicarbonate and hydriodic acid are formed, the latter is then decomposed by the oxygen, as hydrogen has greater affinity for oxygen than for iodine.

If, then, we see certain tumours or swellings cured by the internal administration of iodine, we are justified in assuming that in them the liberation of iodine, which I have just demonstrated to you as resulting from the presence of carbonic acid and protoplasm, goes on continually as long as potassium iodide is circulating in the blood, and that consequently the morbid cell growth or the micro-organisms which give rise to this growth are gradually destroyed. The disturbances of nutrition throughout the body, as I shall show later on, can be explained from this standpoint; whereas if regarded in connection with unchanged potassium iodide, everything remains obscure. To anyone acquainted with the subject it need hardly be said that this liberation of iodine in some tissues is followed by the formation of new compounds; this holds good with regard to other elements, as has been accurately proved in other organic reactions.

For many therapeutic purposes it is immaterial whether physicians prescribe free iodine or potassium iodide. They are able to accomplish more with the latter simply because it can

be given for a longer time without the digestive organs being affected in the way that they are with iodine. In other respects the action of the two drugs appears to be very similar.

Charteris describes the following case :[1]—A woman aged thirty-five suffering from a rheumatic affection, had a solution of POTASSIUM IODIDE, two drachms to six ounces, prescribed for her, of which she took a tablespoonful three times daily—a dose, that is, of about 0·6 gramme (10 grains). After the first dose violent catarrh of the conjunctiva and the nasal mucous membrane set in, with a papular eruption all over the body, itching, and a bruised feeling. All this disappeared in from twelve to twenty-four hours after the medicine was discontinued. The patient had shown this special idiosyncrasy in the case of potassium iodide before. Charteris now gave her TINCTURE OF IODINE, simply as an experiment. When the dose was increased to twenty drops, exactly the same symptoms occurred as before.

Bernatzik gave a patient 1·35 grammes (20 grains) of iodide of iron in twenty-four hours, and tested both the urine and the fæces for its constituents. In the former he found no iron, only iodine ; in the latter only iron and no iodine. He concluded from this that the salt is decomposed in the body. Melsens noticed the same thing after injecting iodide of iron into the pleural or peritoneal cavities.

All this corresponds with the chemical character of iodine, which, unlike any other element, changes from one compound to another, and from one group to another so long as the surrounding conditions offer any possibility of so doing : its therapeutic action probably rests on this fact. That iodine does not readily produce poisonous effects is probably due to the alkaline reaction of the blood, with the alkaline bases of which it readily combines, and to the ready solubility and diffusibility of its salts, which render its continual excretion—especially by the kidneys—possible.

Many points still remain obscure and unexplained under the hypothesis I have advanced, for instance the relief of neuralgia or of bronchial asthma by potassium iodide. When the neuralgia is due to a syphilitic exostosis, or to

[1] Prof. Charteris, "On the Identity of the Action of Iodine and Iodide of Potassium," 'Lancet,' 1882, vol. i, p. 729.

neuritis, or to rheumatic irritation, we can understand the action; but there are also cases due to no such cause which are cured or improved by the use of potassium iodide. We must be better instructed in the pathology of these disorders before we can be expected to explain satisfactorily the results of their treatment.

We have, perhaps, another point to consider in the therapeutic effects—especially the so-called absorbent ones—of the iodides. These bodies in the diluted form in which they circulate in the blood seem to have a stimulating influence upon the leucocytes; their number in the blood is increased, whilst their migration from the blood-vessels into the tissues also becomes more active.[1] We have already seen that the absorption of solid matter may depend upon the presence of a large number of these wandering cells.

The immediate effect of potassium iodide in the remittent fever of syphilis[2] is very striking, though in other similar fevers no such result occurs. This compels us to assume that the active agent in the causation of syphilitic fever is a well-defined and peculiar substance which is formed in certain syphilitic inflammations, and which—either itself or the micro-organism which gives rise to it—can be made less virulent or rendered innocuous by potassium iodide.

The secretion of milk is distinctly lessened by potassium iodide. This fact has been observed both in clinical practice and in the case of animals.[3] The decrease does not merely concern the quantity of water, but includes all the constituents of the milk. This may correspond with the atrophy of the breasts, and also of the testicles, which has sometimes been known to follow the prolonged use of potassium iodide. It is surprising to find in connection with this, that preparations of iodine, especially the tincture, increase the menstrual flow. The early onset of menstruation, or its reappearance when it

[1] R. Heinz, 'Berl. klin. Wochenschr.,' 1890, s. 1186.

[2] Duméril, 'Gaz. des. Hôp.,' 1851, Nos. 40, 46, 62; Ch. Bäumler, 'Arch. f. klin. Med.,' 1872, Bd. ix, s. 397.

[3] M. Stumpf, "Ueber die Veränderungen der Milchsecretion unter dem Einflus einiger Medicamente," 'Arch. f. klin. Med.,' 1882, Bd. xxx, s. 201.

has been absent, has been reported to have occurred under its use.

Potassium iodide when given internally also promotes the more rapid elimination of poisonous metals, especially mercury and lead. Its use is based on the theory that their albuminous compounds dissolve with comparative readiness in potassium iodide.

I have here a very dilute, clear solution of egg-albumen in water, to which I add a few drops of lead acetate. The solution becomes cloudy at once, and yields a precipitate of lead albuminate. I put 10 c.c. of this latter in two small flasks, and pour into the one 5 c.c. of a 10 per cent. solution of potassium chloride, and into the other a similar quantity of a 10 per cent. solution of potassium iodide. I place both of the flasks in boiling water. The former becomes opaque from the complete coagulation of the albumen; the other is not more clouded than before. Potassium iodide has consequently, even under difficulties, kept the albuminate of lead in a state of solution.

This corresponds with the results obtained in the treatment of men or animals suffering from lead or mercurial poisoning. Since the year 1849 potassium iodide has been recommended for the treatment of these disorders.[1] Its usefulness has been confirmed in various ways. The quantity of metal eliminated by the kidneys is increased under the administration of potassium iodide.

Many individuals can take potassium iodide for a considerable time without experiencing any unpleasant effects; with others these effects are produced even by small doses. This peculiar susceptibility of individuals differs also with regard to the kind of SECONDARY EFFECT which results from the use of the remedy.

Among these secondary effects, included under the term IODISM, acute catarrh—with its sequelæ—is the most frequent. This may extend to the mucous membrane of the larynx, of the bronchial tubes, of the sphenoidal sinuses, of the antrum,

[1] M. Melsens, 'Mémoire sur l'emploi de l'iodure de potassium,' &c., Bruxelles, 1865; K. Oettingen, "Heilung der Bleidyskrasie durch Jodkalium," 'Wien. med. Wochenschrift,' 1858, s. 97; A. Annuschat, 'Arch. für exper. Path. und Pharmak.,' 1879, Bd. x, s. 261.

or to the conjunctiva and lachrymal apparatus; the accompanying headache may be quite unbearable.[1] All these symptoms may be caused by a single dose of less than a gramme (15 grains), but they all disappear when the remedy is discontinued.

If laryngeal ulcers are present, acute œdema of the larynx may be developed by the use of potassium iodide; in tuberculosis of the lungs, hyperæmia and hæmoptysis with increased expectoration may be induced.[2] This irritation of the mucous membranes is very readily set up where retained secretion, abrasions, ulcers, &c., present favorable conditions for putrefaction and decomposition.[3] But even when the larynx is free from ulceration, acute œdema of the larynx has been known to follow the use of potassium iodide.[4]

Salivation may also occur. Digestive disturbances are not frequent,—in fact, the appetite is sometimes increased. In healthy individuals after taking 1 to 3 grammes (15 to 45 grains) daily, the secretion of urea has diminished as much as 15 per cent.[5] On the other hand, von Boeck found no noticeable change in the quantity of urea secreted by a syphilitic patient in whom nitrogenous equilibrium was established, who had taken 1 gramme (15 grains) of hydriodic acid, *i. e.* 1·49 grammes (22 grains) of iodine, for six days. It has, however, been noticed that some patients undergo considerable emaciation after the long-continued use of potassium iodide. As yet it is impossible to explain these contradictory results.

Cutaneous eruptions, with or without fever, are comparatively frequent after the use of potassium iodide; they commence as a simple redness, but may become petechial or vesicular.

Two instances have been reported from which it would appear that ammonium iodide acts much more quickly in

[1] Boinet, 'Iodothérapie,' 2 edit., 1865, p. 72; M. Bresgen, "Zwei Fälle von schwerem Jodismus," 'Centralbl. f. klin. Med.,' 1886, s. 153.

[2] A. Groenouw, 'Therap. Monatshefte,' 1890, s. 105; A. Rosenberg, 'D. med. Wochenschr.,' 1890, s. 825.

[3] Oppenheimer, 'Therap. Monatshefte,' 1889, p. 537.

[4] G. Sticker, 'Münch. med. Wochenschr.,' 1888, No. 37.

[5] Fubini, 'Untersuch. z. Naturl. d. M.u. d. Tiere,' 1883, Bd. xiii, s. 111.

producing these cutaneous eruptions than the sodium or potassium salt.[1] This is instructive in so far as ammonium iodide is more readily resolved into its elements than any other salt of iodine. It soon deliquesces when exposed to the air, giving off ammonia and iodine. It is evident that at first $NH_3 + HI$ is formed from the NH_4I, and that the hydriodic acid is then resolved by the oxygen of the air into water and iodine.

In addition to the symptoms described above, irritation of the kidneys or of the nervous system may occur, though with less frequency. Paræsthesia, spasms, painful swellings, and fever have been mentioned in connection with the latter.[2] Although all these secondary effects of potassium iodide disappear when the remedy is discontinued, and although laryngeal œdema—a most dangerous complication—is fortunately very rare, yet they necessitate the greatest watchfulness on the part of the physician when he prescribes potassium iodide for a patient who has not previously taken it. However, these injurious effects of the remedy generally become apparent after the first few doses.

In considering the mode of development of these conditions we get some explanation of what is indicated by the obscure term "idiosyncrasy." Certain chemical conditions occur in the body by which potassium iodide can be resolved into hydriodic acid, and probably into free iodine; and we need only suppose that these conditions exist in a greater or less degree quantitatively in different individuals in order to understand, from actual facts, how iodism is produced. I have already endeavoured to prove that such a condition exists in the power which protoplasm in the presence of carbonic acid possesses of oxidising and resolving chemical compounds. The protoplasm of the glands and its products are especially adapted for this, as glandular organs exist in all parts of the economy, and it is in these organs that iodism is most readily developed. Another factor appears to take part in the process, namely, the salts of nitrous acid, the nitrites.

[1] Duffey, 'Dublin Journ. of Med. Science,' 1880, vol. lxix, p. 273.

[2] E. Malachowski, "Beitrag zur Kenntniss der Nebenwirkungen des Jods (Jodskaliums)," 'Therap. Monatshefte,' 1889, s. 162.

Normal human saliva decomposes an acidulated solution of potassium iodide, as you can see from the experiment I here show you: nasal mucus has the same property. If the saliva is heated this property is not destroyed, and it is consequently attributed to the presence of nitrites; these, as is shown by this simple experiment, are also decomposed outside the body by carbonic acid in the presence of potassium iodide, and the nascent oxygen liberates the iodine. If this takes place, whether with or without simultaneous activity of the lymphoid cells of the external air-passages, then direct irritation will be produced by the iodine. Most likely similar conditions exist in the skin and other tissues which are affected by iodism. The acne pustules[1] which occur after taking potassium iodide contain compounds of iodine. The latter are also found in the perspiration, as can be proved by collecting it with blotting-paper and digesting this in water.

How far this explanation is valid has been tested by administering sulphanilic acid[2] and large doses of sodium bicarbonate[3] in cases of iodism. This acid, whose formula is $C_6H_4.NH_2.SO_3H$, combines with the nascent nitrous acid to form the corresponding diazo-compound, and is not itself poisonous. When given in doses of from 4 to 6 grms. (60 to 90 grains) shortly after the appearance of iodism, it often either cured or alleviated the symptoms. Further, large doses of sodium bicarbonate, 10 to 12 grms. (150 to 180 grains) daily, render the fluid of the body more strongly alkaline, and thus lessen the possibility of the formation of hydriodic acid and iodine.

If in some cases this extraordinary susceptibility to iodide of potassium shows itself, we notice in others, that very large doses are often extremely well borne. With reference to such cases I may mention that a female patient here in Bonn suffering from psoriasis, took 1920 grms. in 102 days,[4]—that is to say, nearly 19 grms. (290 grains) daily.

The largest quantity taken in a day amounted to 28 grms.

[1] Adamkiewicz, 'Charité Annalen,' 1876, Bd. iii, s. 381.

[2] Ehrlich, 'Charité Annalen,' 1885, Bd. x, s. 129; Krönig, ibid., s. 177.

[3] Röhmann und Malachowski, 'Therap. Monatshefte,' 1889, s. 301.

[4] Doutrelepont, 'Niederrhein Ges. f. N. u. H.,' November 21st, 1887.

(420 grains), and this was repeated for eight days. Haslund[1] gave as much as 50 grms. a day, when symptoms of poisoning naturally manifested themselves. He thinks that when more than 40 grms. are given in a day great watchfulness is necessary.

The EXCRETION of potassium iodide by the different secretions and excretions, and the detection of its presence in the various tissues of the body, have been the object of many researches. It was to be expected that such a soluble salt, one so readily diffusible, and of which the presence is so easily recognised, would appear and be readily detected everywhere in the tissues. This proved to be the case. A few minutes after its absorption by the stomach the iodide was found in the urine and in the saliva, whilst the metalloid could be found in the body for a period of 45 to 150 hours,[2] according to the dose administered. It is easily detected when given in large doses. A few drops of chlorine water are added to the urine or saliva, and then a little cold starch mucilage. The iodine is displaced by the chlorine, and gives a blue colour to the starch.

The recognition of very small quantities of iodine requires a somewhat more elaborate process. The liquid is mixed with excess of caustic soda, evaporated down, and carefully incinerated. The residue is treated with a little water, and the solution tested for iodine. Carbon bisulphide or chloroform is coloured red by slight traces of free iodine, the amount of which is too small to give a blue colour to starch.

Less unanimity exists with regard to the ABSORPTION by the unbroken skin, of iodine when applied in the shape of OINTMENTS or solutions, than there is in the case of its excretion. So far as the ointment is concerned, a fresh investigation was carried out in my laboratory, with the following result:—If we use lard, vaseline, or lanoline as a basis, and rub the ointment well in, a perceptible, though small, portion of the potassium iodide passes into the circulation, and may be found in the urine by mixing this with caustic soda and incinerating, treating the residue with water, and then

[1] Haslund, 'Vierteljahrschr. f. Dermat. u. Syph.,' 1887, s. 671.

[2] Rózsahegyi, 'Jahresber. über die Fortschritte der Pharmakogn., Pharmacie, und Toxikologie für 1878,' s. 564.

adding one drop of fuming nitric acid; on shaking this solution with carbon bisulphide it readily absorbs the liberated iodine, and acquires a deep violet colour.[1]

The contradictory statements with regard to the absorption of potassium iodide from baths and compresses, require further investigation before the matter can be decided.[2]

When ADMINISTERED INTERNALLY potassium iodide is usually given as a solution in water without any other addition, in doses of 0·1 to 2 grammes (1½ to 30 grains). The drug must be pure, and the presence of iodic acid should be especially guarded against. The tests for this I have already demonstrated to you. If the potassium iodide cannot be given by the mouth, we may then prescribe it subcutaneously. But we must not use very concentrated solutions, as one stronger than 1 : 3 is very painful, and causes suppuration and necrosis of the skin. In case of need a solution of the potassium iodide may be injected by the rectum, where it is rapidly absorbed.

The officinal OINTMENT OF POTASSIUM IODIDE contains, according to the German Pharmacopœia, 20 parts of potassium iodide dissolved in 15 of water, and mixed with 165 parts of lard. It, moreover, contains SODIUM THIOSULPHATE, or sodium hyposulphite, the formula for which is $Na_2S_2O_3$. The reason for adding this is, that potassium iodide decomposes under the influence of fat and air, and the ointment becomes yellow. The sodium thiosulphate combines with any iodine which may be liberated, and forms sodium iodide and sodium tetrathionate ($2Na_2S_2O_3 + I_2 = 2NaI + Na_2S_4O_6$), thereby keeping the ointment white, a condition required by many physicians. In my opinion the small quantity of free iodine mixed with lard and potassium iodide only renders the ointment more efficacious.[3]

[1] A. Peters, 'Centralbl. f. klin. Med.,' 1890, s. 937.

[2] A. Röhrig, "Untersuchung. über die flüssige Hautaufsaugung," 'Arch. d. Heilkunde,' 1872, Bd. xiii, s. 341; R. Fleischer, 'Untersuchungen über das Resorptions-vermögen der menschlichen Haut,' Erlangen, 1877; G. Bachrach, ref. 'Centralbl. f. d. med. Wissenschaft., 1879, s. 24; P. Guttmann, 'Zeitschrift f. klin. Med.,' 1887, Bd. xii, s. 276.

[3] The Unguentum Potassii Iodidi ('Ph. Brit.') consists of 16 parts

A former method of making the ointment with vaseline has fallen into disuse, as dispensers did not always know how to prepare it of a uniform strength. This preparation was not liable to turn yellow.

SODIUM IODIDE, NaI, is another of the officinal salts; it is a dry, white, crystalline, deliquescent powder, and has a milder taste than the potassium salt. It is soluble in 0·6 part of water or three parts of alcohol. According to the German Pharmacopœia, it must not contain less than 95 per cent. of the anhydrous salt.

It is more easily decomposed than potassium iodide. When fused with charcoal with access of air, it is, unlike potassium iodide, largely converted into sodium carbonate, and on exposure to light even at the ordinary temperature, it is coloured yellow, from the liberated iodine, more readily than with the potassium salt.

Sodium iodide was included in the Pharmacopœia because clinical experience showed that a prolonged use of it was more readily tolerated—especially where there was cardiac weakness—than was the case with the potassium salt. It is administered in the same way and in the same doses as the potassium salt. The same tests may be employed to determine its purity. It differs from the potassium salt in giving no precipitate with tartaric acid.

Most German saline springs contain, together with bromides, small quantities of the iodides of the alkalies; Krankenheil in Bavaria contains 0·015 gramme NaI in 10 litres of water, together with some soda. Saxon in Switzerland sometimes contains as much as 1·78 grammes in 10 litres, but this quantity varies, and occasionally from some unknown reason disappears altogether. This water also contains calcium carbonate and sodium and magnesium sulphate.

SODIUM IODATE, $NaIO_3$, is only of theoretical interest. It is a white salt with a neutral reaction, soluble in 15 parts of water. In the animal body it gives up its oxygen and appears as iodide in the urine: the iodate only appears there when the drug is given in large quantities.

Sodium iodate is an antiseptic owing to its parting readily

of potassium iodide and 1 of potassium carbonate dissolved in 14 parts of water and mixed with 110 parts of benzoated lard (transl.).

with the oxygen which is loosely combined in it, and to the iodine being subsequently liberated. It paralyses the nerve-centres in the same way as a true narcotic poison, lowers the temperature considerably, and when injected subcutaneously produces inflammation of the mucous membrane of the stomach and intestines, together with fatty degeneration of the liver and other organs.[1]

Thus we have IODINE, SODIUM IODIDE, SODIUM IODATE, and IODOFORM presenting the same qualitative characteristics, all of which point to the liberation of iodine in the different organs, and differing only with regard to their doses, the rapidity of their absorption, and the readiness with which they enter into new combinations.

[1] For details see C. Binz, 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. viii, s. 309, und 1880, Bd. xiii, s. 113; R. Böhm, 'Sitzungsber. d. Ges. z. Beförderung d. ges. Naturwiss.,' Marburg, 1882, No. 4.

X.

Experimental facts bearing upon the production of Narcosis—Narcotics cause opalescence or cloudiness in fresh sections of the brain—Rôle *of the halogens in their compounds—Contraction of the blood-vessels in the brain—Lowering of the blood-pressure — Atropine — Stimulation of the brain—Ancient and modern statements—General description of its poisonous effects—Paralysis of the peripheral nerves —Experiment upon the cardiac branch of the vagus—Dilatation of the pupil—Use in therapeutics—Atropine and Muscarine—Atropine as a poison—Therapeutic antagonism between Morphine and Atropine—Hyoscyamine and Hyoscine.*

Having now discussed the chief remedies employed as narcotics, I proceed to bring together some of the points connected with them, from which we may perhaps arrive at an explanation of the way in which their effects are produced.

Morphine is the only vegetable base in the Pharmacopœia which has a reducing action strong enough to remove oxygen energetically from oxidised compounds. I have here a colourless solution of iodic acid, HIO_3, to which I add a little morphine ; it at once becomes a deep yellow from the separation of iodine. This is due to the fact that the morphine has formed hydriodic acid from iodic acid, and this hydriodic acid decomposes the remaining iodic acid in the manner already explained :

$$HIO_3 + 5HI = 3H_2O + 3I_2.$$

The questions whether, and how far, this property of morphine influences the cells of the brain cannot as yet be

definitely answered. The following microscopical changes are, however, points with which we are immediately concerned.[1]

This rabbit has been bled to death by opening the carotids, and its brain has been quickly exposed. With a sharp scalpel I quickly remove a few small pieces of the cerebral cortex, and tease them out on a slide in a drop of 1 per cent. solution of perfectly NEUTRAL hydrochlorate of morphine. I now put them in a moist chamber which is kept at a temperature of 37°—38° C. (98·6°—100·4° F.), and allow them to remain there for three hours. A cover-glass is then put over them, and they are examined with a high power under the microscope. A control preparation of the same tissue has been placed under the same conditions in a 1 per cent. solution of sodium chloride. This last preparation under the microscope looks clear and transparent, and the nuclei especially show no change; whilst the former preparation has become cloudy, its nuclei appear granular, and the cell walls more distinct.

This action of morphine, first described by me, was investigated elsewhere,[2] but my results were apparently not confirmed. By carrying the experiment, however, somewhat further, it has been shown[3] that morphine acts exactly as I said it did; and a very simple method has been found by which this may be rendered clear even to anyone who has had but little practice in the use of the microscope. Although I examined the preparation only with high magnifying powers, and recommended this plan, it would be better for anyone not skilled in microscopical work to use low powers; the clouding of the morphine preparation then shows itself most distinctly, the nuclei stand out—when the mirror is properly adjusted—like sharp points, whereas in the control preparation they are hardly visible.

The officinal salts of atropine, cocaine, and pilocarpine act similarly to sodium chloride upon a fresh section of the

[1] C. Binz, 'Arch. f. exper. Path. u. Pharmak.,' 1877, Bd. vi, s. 312, und 1880, Bd. xiii, s. 163.

[2] H. Ranke, 'Centralbl. f. d. med. Wiss.,' 1887, s. 610.

[3] W. Kochs, "Zur Wirkung der Nervengifte auf freipräparirte Nervensubstanz," 'Centralbl. f. klin. Med.,' 1886, s. 889.

cerebral cortex; the officinal neutral salts of strychnine and quinine act in the same manner as morphine.[1]

The opalescence or clouding of the freshly prepared brain cells is extremely distinct, and is at once visible with any magnifying power if they have been exposed to the vapour of chloroform, or treated with a neutral solution of chloral hydrate instead of morphine. These changes are depicted in the accompanying illustrations.

FIG. 6.

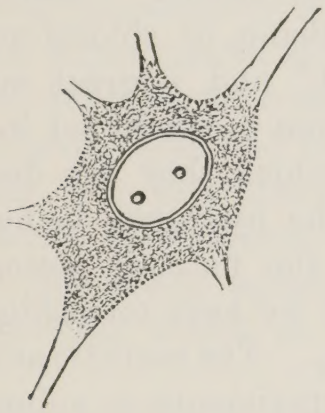
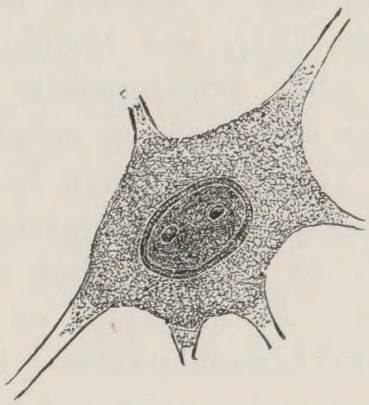


FIG. 7.



The whole process appears to resemble a coagulative necrosis, such as we see when neutral substances, which are poisonous to protoplasm, act upon large transparent infusoria, particularly when the action is feeble at first, and afterwards more marked. The protoplasm soon becomes somewhat clouded or opaque, and the movements are sluggish; later the protoplasm becomes granular and its movements cease. Recovery may occur from the first stage if the poison is quickly washed away, but not from the latter stage. I compare the one to the sleep, the other to the death of the cell; resolution may take place from commencing, but not from complete coagulation.

When we consider the HALOGEN COMPOUNDS which have narcotic properties, we are struck with the fact that the proportion of halogen in them is very considerable. Chloroform has 89·1 per cent. of chlorine; bromoform, which has a similar action, contains 94·8 per cent. of bromine; iodoform

[1] For an account of corresponding changes in the nerve-endings of a lizard after curare poisoning see W. Kühne, 'Untersuchungen a. d. Physiol. Inst. zu Heidelberg,' 1878, Bd. ii, s. 208.

96·7 per cent. of iodine. There are 67·3 and 77·7 per cent. of bromine in potassium bromide and sodium bromide (anhydrous). The soporific and soothing properties of these bodies depend upon the presence of the halogens. This is shown in sodium bromide, for here one constituent, sodium, has no influence whatever of that kind, and this is still more marked in the case of some other halogen compounds.

Glycerine as such has no effect upon the nervous centres ; trichlorhydrine—$C_3H_5Cl_3$—a glycerine in which three atoms of hydroxyl are replaced by three atoms of chlorine, has a marked narcotic action.[1] Marsh gas, or methane, CH_4, and trichlormethane, or chloroform, $CHCl_3$, acetic acid, trichloracetic acid,[2] and a great many other chlorine and bromine substitution products act in the same way. The hydrocarbon from which they are derived may have disappeared altogether, the hydrogen being replaced entirely by chlorine, but still the narcotic action is very distinct. As examples of this we have tetrachlormethane, CCl_4, and hexachlorethane, C_2Cl_6. The narcotic action of the former was demonstrated by experiments on animals and on fifty-two patients, and was so marked that the experimenter[3] even recommended it instead of chloroform ; whilst the action of the latter compound was shown in experiments which were being conducted in my laboratory [4] when this work was passing through the press. Narcotic effects can be obtained also from the fumes of pure chlorine, bromine, and iodine.[5] This has also been observed in cases of poisoning by hypochlorous acid.[6]

Sodium CHLORIDE, which in our bodies is only decomposed

[1] A. Romensky, 'Arch. f. d. g. Physiol.,' 1872, Bd. v, s. 565.

[2] G. Bodländer, 'Centralb. f. klin. Med.,' 1884, s. 249 ; 1885, ss. 105 u. 199.

[3] Prothero Smith, 'Lancet,' 1867, vol. i, p. 660, *et seq.*

[4] C. Binz, "Beiträge zu pharm. Kenntniss des Halogens," 'Archiv f. exper. Pathol. u. Pharmakol.,' Bd. xxxiv, s. 185.

[5] C. Binz, "Narcotische Wirkungen von Jod., Brom., und Chlor.," 'Arch. f. exper. Path. und Pharmak.,' 1880, Bd. xiii, s. 139 ; K. B. Lehmann, 'Arch. f. Hygiene,' 1887, Bd. vii, s. 265.

[6] Simonson, 'Casper's Wochenschr. f. d. ges. Heilk.,' 1837, s. 123 ; Cameron, 'Dublin Quart. Journ. of Med. Science,' 1870, vol. xlix, p. 116.

in the acid glands of the stomach, has no action at all upon the nerve-centres. Sodium BROMIDE, on the other hand, paralyses them. Sodium IODIDE has a similar action,[1] even when given in the small doses in which sodium chloride is altogether inert. Sodium FLUORIDE[2] behaves in the same way. Drowsiness, great weakness, somnolence, with "free respiration and vigorous heart action," are said to be the effects produced both in men and animals. Sodium iodide has the feeblest action of the three,—that is to say, it must be given in larger doses to produce the same result. This is what the general character of iodine would have led us to expect.

Certain experimental facts appear to show that the haloid soporifics undergo some change in the tissues of the brain, the acid being liberated from these haloid bodies, and then paralysing the protoplasm. I will not here discuss the point; these experiments do not indicate which element or group is the active agent, or what change takes place in those soporifics which do not contain any halogen constituent.

The view is still occasionally advanced that soporifics act by causing ARTERIAL ANÆMIA OF THE BRAIN, and that this result is due either to a contraction of the blood-vessels or to a fall in the blood-pressure. Certain conditions seem to support this view. Thus chlorotic individuals, in whose brains there must be a deficient supply of blood, have to struggle all day against sleep; and, again, loss of blood produces drowsiness. On the other hand, our thoughts are most rapid when the heart beats strongly, when the face is slightly flushed, and when the brain is well nourished with a continuous supply of blood.

The strong belief in this view which I have heard expressed in conversation, and also seen in print, induced me to undertake certain experiments[3] in order to test the

[1] R. Böhm, 'Arch. f. exper. Path. u. Pharmak.,' 1876, Bd. v, s. 340.

[2] Tappeiner, 'Arch. f. exper. Path. u. Pharmak.,' 1889, Bd. xxv, s. 203; Hugo Schulz, ibid., s. 326; O. Hewelke, ref. 'Schmidt's Jahrb.,' 1889, Bd. ccxxii, s. 129; O. Nasse und C. Frese, in Doctordiss. Rostock, 1889, s. 39, *et seq.* With regard to Tappeiner's work see p. 201.

[3] C. Binz, "Zur Wirkungsweise schlafmachender Stoffe," 'Arch. f.

truth of the matter. From these experiments I select the following:

A piece of the parietal bone, 18 mm. in diameter, was removed with a trephine from a healthy dog, and the dura mater carefully exposed. The dog had previously been anæsthetised, and had received a subcutaneous injection of 1·5 grms. of chloral hydrate. The hæmorrhage was very slight. The surface of the brain could be closely watched during the profound sleep as the heart and lungs continued to act in a perfectly normal manner. There was great injection of the capillary vessels. The substance of the brain was rose-red. The dog soon awoke from its sleep. He lay bound on the table, but he lifted his head and responded when called. No change in the appearance of the brain was observed. This was inspected again at the end of three hours, having been in the meanwhile covered by the scalp, which was stitched together over it. The condition of all the blood-vessels had undergone little change. The animal was again anæsthetised and kept under observation for half an hour. It was sleeping gently, the heart's action and breathing were regular, but there was not the slightest change in the condition of the vessels.

A large rabbit was put under the influence of ether, and the vault of its cranium trephined. As soon as the animal had completely recovered it was again narcotised with ether. The vessels of the dura mater presented the same appearance both before and during the deep sleep which was induced. Two hours afterwards, during which time the animal had been lively and running about, the dura mater was removed, and the animal etherised once more. The blood-vessels showed absolutely no change even when examined with a lens.

In both cases a drawing was taken of the smallest vessels that were visible in a portion of the pia mater; these vessels were again examined during the deep narcosis, and their condition then compared with the drawing. This method

exper. Path. u. Pharmakol.,' 1876, Bd. vi, s. 310, und 1880, Bd. xiii, s. 157: see also M. Arloing, 'Compt. Rendus de l'Acad. d. Sciences,' 1879, Bd. lxxxix, s. 245; W. Panhoff, 'Arch. f. Anat. u. Physiol.' (Physiol. Abt.), 1881, s. 419.

gave a definite standard by which to estimate any change that took place. None of these small vessels disappeared from view when the narcosis was fully established ; it was only after it had lasted for some time that the INACTIVE brain was less injected than before, and became pale ; thus demonstrating that the condition which had been so often spoken of as the cause of narcosis was really dependent upon it.

Of the remaining experiments bearing on this question I need only refer to the most recent ones, in which the action of SODIUM FLUORIDE has been investigated. Tappeiner in his first experiments came to the conclusion that the narcotic action of sodium fluoride was chiefly due to lowering of the blood-pressure brought about by paralysis of the vaso-motor centres. In consequence of the doubts which I expressed concerning this he again investigated the matter, the result being that he confirmed my opinion. Symptoms "of the direct effect of sodium fluoride on the central nervous system"[1] were produced before there was the slightest sign of any lowering of the blood-pressure.

The fact that the narcosis induced by chloroform is independent of the condition of the cerebral vessels has been proved by direct observation on the human subject.[2] In a patient, a portion of whose cranium had been destroyed, the condition of the vessels observed during the narcosis, remained absolutely unchanged, when he recovered consciousness and sensibility.

As we have seen, the ends of the motor nerves of the trunk and limbs may be temporarily paralysed by curare, and, as we shall see later, the cardiac ends of the vagus are affected in the same way by atropine. No one could possibly think of asserting that such conditions arose from a diminished supply of blood to the nerve-endings, or from a lowering of the blood-pressure. The only possible view is that they result from a direct action on the nervous protoplasm.

[1] Namely, marked signs of bodily weariness and "diminished reflex irritability" (Tappeiner, 'Arch. f. exper. Path. u. Pharmak.,' 1890, Bd. xxvii, s. 47). The incorrect remarks with which the author prefaces the above admission, are of no consequence, and are disproved by his own results.

[2] Carle und Musso, ref. 'Centralbl. f. klin. Med.,' 1886, s. 602.

This, then, is the state of the case with regard to our knowledge of the action of soporifics, ranging from sodium bromide on the one hand, to chloroform on the other. They produce their effect by direct action on the cerebral tissue.

ATROPINE causes paralysis, though it does not act on the same organs as the narcotics we have previously discussed. The officinal salt ATROPINUM SULPHURICUM, ATROPINÆ SULPHAS, sulphate of atropine, is a white crystalline powder soluble in an equal part of water, and in three times its weight of alcohol, forming a bitter neutral solution: it is almost insoluble in ether and chloroform. It is obtained from the *Atropa belladonna*, common dwale, or deadly nightshade, of the Natural Order Solanaceæ, which is known in Germany by the names of Tollkirsche, Tollkraut, Tollwurz—names derived from the action of the plant upon the human brain. It was named belladonna as early as the sixteenth century, professedly on account of its external application as a cosmetic to give brightness to the eyes by dilating the pupils; the word atropa was added by Linnæus in remembrance of the Fate whose business it is to cut the thread of life. We cannot trace with certainty any mention of the plant in the writings of the ancients: with physicians of the Middle Ages it figures as *Solatrum furiale;* and L. Fuchs, of Tübingen, botanist and physician, described it in 1542 as *Solanum somniferum*, or Dollkraut; whilst Matthiolus, a little later, called it *Solatrum majus*.

As in the case of so many other medicinal plants, belladonna was at first only regarded as a poison; it was afterwards much used as a drug, but came into disrepute in the period of

reaction against all medicinal remedies. Later, its action in the form of atropine sulphate was scientifically studied by experiments upon animals and men, its chief constituent, atropine, having been previously discovered in 1832 by Mein, and simultaneously by Geiger and Hesse. Since that time it has become indispensable in therapeutics, and an important substance in toxicology.

Let us first—following the course of its historical evolution—consider the poisonous properties of the plant and its alkaloid. We must confine ourselves to human beings, for rabbits, &c., are somewhat immune to the action of the plant or even of atropine (a fact which has long been known[1]), so that we can only illustrate the more subtle actions of the drug with them.

Our experience with regard to the poisonous action of belladonna and atropine on man is, however, very large. In former times this chiefly arose from poisoning by the beautiful brilliant black and sweet berries, which ripen in autumn. Cases of poisoning from this cause also occur at the present time, but they generally arise from atropine, which is prescribed chiefly by the oculists, and is thus easily accessible, and may be taken either designedly or by accident.

Violent maniacal excitement is the first prominent symptom. "Baccæ ipsæ devoratæ sumentes dementant et in furorem agunt, adeo ut dæmoniaci facti videantur," was the account given by Matthiolus—hence the name Tollkirsche, whilst his contemporary Dr. Johannes Weyer, physician in ordinary to the Duke of Cleve, who was the first man to make a courageous stand against witchcraft, describes,[2] in the sixteenth chapter of his work entitled 'De naturalibus pharmacis somniferis, quibus interdum illuduntur Lamiæ,' the consequences of a boy eating belladonna berries: "primum cæpit furiose agere," &c.

Further, in those good old times various jokes were played by means of belladonna. We learn from Matthiolus how

[1] J. Fr. Gmelin, 'Abhandlung von giftigen Gewächsen,' Graz, 1776, s. 118.

[2] J. Wierus, 'De Præstigiis Dæmonum et Incantationibus ac Veneficiis Libri Sex Aucti et Recogniti,' Basel, 1568, s. 273.

"wonderful is the power of the root, for if one drachm of it, roughly bruised, be macerated in wine and strained, then anyone who partakes of this on an empty stomach is totally unable to eat anything afterwards. . . . . It is a great joke to give this wine to some hungry sponger, and then place him at a well-spread table, for owing to the dryness of his mouth and throat he is quite unable to eat anything."

A recent author[1] thus graphically describes the symptoms of atropine poisoning in a soldier aged twenty-three:—Violent delirium accompanied with visions and hallucinations, alternately of a cheerful or terrifying character. The patient constantly struggles to leave his bed, for he is haunted by ghosts which occupy the corners of the room. He then sits up in bed, laughs loudly, talks nonsense incessantly, gnashes his teeth violently. His face is spasmodically distorted, and he beats the air with his arms. He begs for cold water, on account of the parched condition and the feeling of constriction in his throat. Swallowing becomes difficult, and fluids trickle partly back again from his mouth. The voice is hoarse. The man refuses medicine, saying it is poison, or else he spits it out again. He becomes tranquil, and coma gradually sets in with redness of the face, stertorous breathing, and grinding of the teeth. Later the urine is passed involuntarily; the patient lies quietly with closed eyes; the lips and face are cyanosed and turgid; the skin dry and flabby; temperature 38·2° C. (100·8° F.), the radial pulse 152, irregular, small, with diminished wave; respiration 36, chiefly thoracic in character, but aided by the auxiliary respiratory muscles. There are convulsive movements in the muscles of the face, forearm, and fingers. When spoken to, the patient slowly opens his eyes, looks round in a dazed manner, but gradually recognises his surroundings and understands questions put to him. He tries to answer, opens his mouth, and moves his lips, but is unable to utter a sound; at the same time he seems cheerful and laughs hoarsely. The tongue is put out slowly and straight; it is very tremulous, dry, and furred. The pupils

[1] Pfuhl, 'Deutsche Zeitschr. f. prakt. Med.,' 1878, No. 50; see also J. Kratter, 'Vierteljahrschr. für gerichtl. Med.,' 1886, Bd. xliv, s. 52, which contains copious references to the literature on the subject.

are dilated to their utmost extent, so that the iris is hardly visible. Sensibility in the arms and face is lessened, and a little later the patient sinks into his former somnolent condition. The cause in this case of poisoning was the employment by mistake of a solution of 1 in 150 of sulphate of atropine in water, two drops of which were placed in each eye EVERY HOUR for three days. The patient speedily recovered.

If I now bring together the symptoms of atropine poisoning in general, they may be arranged as follows :—Delirium and hallucinations, mostly of a disagreeable and distorted kind ; attacks of mania, at times with an inclination to bite ; great restlessness, the head hot and flushed, the eyes staring and bright, with dilated motionless pupils ; the sight impaired, whilst chromatopsia and diplopia may be present ; throbbing of the carotids ; dryness of the mouth and throat, thirst, difficulty in swallowing, a disagreeable taste, vomiting, hoarse voice ; very rapid, and later on laboured respiration ; quick, small pulse ; scarlatinoid redness of the dry skin, especially of the head and neck ; coldness of the extremities, low temperature in the rectum, swollen abdomen, costiveness ; the urine diminished in quantity and containing albumen and fibrinous casts ; spasms of the face, extremities, and trunk, cyanosis of the skin and lips, gradual transition of the cerebral excitement into complete paralysis, and finally, paralysis of the respiration and heart.

This picture may be varied not only by the absence of some of the chief symptoms, but also by the fact that some of the symptoms may be quickly followed by others of a contrary character. The heart-beat may be rapid and vigorous, and a little later extremely slow and hardly perceptible. Again, at the commencement of the poisonous symptoms the number of respirations may be decreased, whilst later they become very frequent. We have in atropine a poison which simultaneously affects many of the nervous tracts and centres. These react to it in different ways : some are stimulated, others paralysed ; some respond quickly, others take a long time. And, further, the secondary effects in the blood, and the subsequent accumulation of carbonic acid, cause peculiar symptoms, which either

coincide with those of the poison or make them indistinct, according as they follow or are antagonistic to them. No particular case, therefore, will present a complete picture of all the symptoms.

In frogs and rabbits the symptoms of cerebral excitement are not at all prominent; in the dog they are more marked, and it is probable that the animal experiences hallucinations. Atropine consequently acts directly upon the seat of the intellectual faculties, that is upon the cerebral cortex. Where this is undeveloped, atropine has no perceptible action. If its stimulating action in the case of human beings extend to the mid-brain, to the so-called spasm-centres and medulla oblongata, convulsions and spasms are set up, which begin in the face and extend to the limbs.

It has been said, and this was confirmed by one case which came under my own observation,[1] that the spasms may apparently altogether subside, and then recur several hours later.

From amongst these poisonous symptoms I will select one group which indicates to us the therapeutic use of the drug; it is the PARALYSIS OF THE PERIPHERAL NERVES. The rapid pulse, the dilated pupil, the dry mouth and throat, the parched skin, the diminished peristaltic movement of the bowels, are all due to this.

Here is an experimental proof as regards the first of these symptoms. I expose the vagus on one side of the neck of a large rabbit, divide it, and gently place the peripheral portion on two electrodes. If I now pass a very feeble faradic current through these, I can feel, by putting my hand on the chest of the animal, that the heart at once ceases to beat. In order that you may see this I introduce a long needle—to which a little white feather is attached—between the ribs into the apex of the heart. We can thus easily count the number of the beats by the movements of the feather; they are 160 in the minute. If we now pass the current through the electrodes which are connected by the exposed nerve, the inhibitory nerve of the heart is tetanised as before; the heart CEASES TO BEAT, and the feather shows only a slight movement, which is due to the continuance of respiration. I break the current in a few

[1] C. Binz, 'Deutsche med. Wochenschr.,' 1879, s. 629.

seconds, so that the animal may not be suffocated. The heart again begins to beat. If I repeat the experiment several times, the result is always the same.

I now inject 0·02 gramme sulphate of atropine in 1 c.c. of water under the skin of the animal's abdomen. Three minutes later I try again to tetanise the peripheral portion of the inhibitory nerve, keeping the coils at the same distance from each other as before, but the heart-beat is merely diminished to about 80 a minute. It is only by moving the coils nearer by several cm. that the heart's action is stopped. Six minutes later I now, as you see, move the coils nearer to each other; the current is so strong that my finger cannot stand it, but the peripheral end of the vagus, which otherwise for several hours would respond to stimulation, is no longer affected by it. Atropine has rendered the nerve insensible to this stimulation, just as chloroform or ether does in the case of the cerebral cortex. The vagus is anæsthetised by its special soporific.

The ENDS OF THE VAGUS, not the trunk, are the parts affected, as is seen by dissecting out a comparatively long piece of the nerve-trunk, and isolating it from the blood which contains atropine. This can, moreover, be proved independently. If I place two fine electrodes upon the back of a healthy heart, between the sinus venosus and the auricles, and then pass a very weak faradic current through them, the heart immediately ceases to beat. A subcutaneous injection of atropine prevents this stoppage also.

The motor end-apparatus of the IRIS reacts in a similar manner. I have previously put one drop of a solution containing 0·1 of a mg. of atropine into the eye of an albino rabbit, and now pass round the animal, which is loosely bound. The one pupil is, as you see, greatly dilated, and the iris shows hardly any change even when concentrated light is thrown upon it. MYDRIASIS is the name given to this condition, from ὁ μύδρος, the glowing block, because the apparently dark interior of the eye allows the rays of light to be reflected from the cornea much more extensively than usual. The eye in which the atropine has not been dropped is unchanged, its pupil contracting at times because the larger amount of light which falls into the other

eye produces reflex action in both, and stimulates the pupil of this eye to increased action. The eye which is under the influence of atropine becomes hypermetropic, and loses its power of accommodation. How is all this brought about? And, primarily, is the effect produced local or central?

It is local, originating in the iris itself, for it is produced by external application much more quickly than when the drug is absorbed by the stomach or skin, even if it is given in much larger doses. The pupil can also be made to dilate on one side only at first, by carefully applying the drug to that side of the eye. The pupil also of the recently excised eye of a frog will dilate under the application of atropine.

The drug may act upon the sympathetic which supplies the radial fibres of the iris, or upon the oculo-motor and ciliary nerves which supply the circular fibres. In the first case the atropine stimulates the nerve-endings of the sympathetic, in the latter it paralyses the endings of the oculo-motor and ciliary nerves. The decision of this question has called forth a series of experiments upon animals, of which I will quote two examples. If we stimulate the oculo-motor nerve of an animal inside the cranial cavity, having previously dropped atropine into the eye, we obtain no contraction of the pupil, though we can still bring this about in the same eye by directly stimulating the sphincters of the iris with the current (Bernstein). If we remove a piece of the sympathetic, and allow the end of the nerve to degenerate for three months, and then drop atropine into the eye, the pupil becomes wider.[1] The atropine can now only act upon the endings of the oculo-motor nerve, and yet it has the same effect as in the normal eye. This drug therefore acts by PARALYSING the endings of the oculo-motor nerve.

Opinions are divided as to whether INTRA-OCULAR TENSION is increased or not after the application of atropine. It has been pointed out[2] that in glaucoma, atropine increases the already existing tension to a dangerous extent. Most probably the state of the case is as follows:[3] Atropine

[1] H. Braun, 'Arch. f. Ophthal.,' 1859, Bd. v, II, s. 112.

[2] Laquer, 'Arch. f. Ophthal.,' 1877, Bd. xxiii, III, s. 149.

[3] F. Stocker, ibid., 1887, Bd. xxxiii, i, ss. 105—158, which contains an excellent bibliography of the subject.

slowly diminishes the intra-ocular tension in animals which are HEALTHY, and have been placed under the influence of curare; but the movements of the pupil do not necessarily depend upon an increase or decrease of the tension; consequently various morbid conditions will influence the amount of tension due to the use of atropine in different ways. If the blood-pressure in general is increased by the absorption of atropine into the system, then the eyeball will be affected by this in an equal degree.[1]

The CHORDA TYMPANI, which is to a large extent a secretory nerve, has been the subject of many experiments. If this nerve is stimulated, a large amount of thin watery saliva will be secreted, the blood-stream of the gland will be accelerated, and its blood will have a brighter colour. If atropine is previously injected into the organ the first of these three results is prevented.[2] Neither the branch of the sympathetic which supplies the submaxillary gland, nor the substance of the gland itself is affected by the action of atropine. We must assume that atropine affects the nerves which control the secretion of saliva in the mouth, throat, and air-passages, and also those which control the perspiration in the skin, very much in the same manner as it affects the secretory fibres of the chorda tympani.[3] Dryness in the mouth, air-passages, and skin is consequently produced. Again, atropine will check the secretion from these organs even after it has been considerably augmented by the use of other poisons, such as pilocarpine.

I can show you this inhibitory action upon the CUTANEOUS GLANDS by means of a very simple experiment. Here (in two tall glass jars) are two healthy strong frogs, one of which was subcutaneously injected two hours ago with 0·005 grm. of atropine, whilst the other was left alone. Both have been since kept in a warm room. The skin of the frog to which atropine was given has remained dry in spite of the animal being in a state of excitement and

[1] Graser, 'Arch. f. experim. Path. u. Pharmak.,' 1883, Bd. xvii, s. 357.

[2] Heidenhain, 'Arch. f. d. ges. Physiol.,' 1872, Bd. v, s. 309.

[3] J. N. Langley, "The Effect of Atropine upon the Supposed Varieties of Secretory Nerve-fibres," 'Journ. of Physiol.,' 1888, vol. ix, No. 2.

trying to climb up the side of the jar; the skin of the other is covered with moisture notwithstanding the fact that it sits quietly at the bottom of the jar.

After smaller doses of atropine the peristaltic movement of the INTESTINES of rabbits is augmented. This is due to paralysis of the splanchnics, and especially of their inhibitory fibres, as on stimulating these there is no diminution of the peristaltic action—that is to say, the action of the atropine produces the same effect here as it does on the peripheral ends of the vagus and on the heart. The sensory and vaso-motor fibres of the splanchnics are not affected by atropine, for on dividing them pain is felt and the blood-pressure falls, even after the administration of the atropine, whilst a considerable increase in the blood-pressure takes place on stimulating the peripheral end. Large doses of atropine, however, also paralyse the motor nerves of the intestines, and put a stop to the peristaltic movement.

The tone of the MUSCULAR COAT OF THE BLOOD-VESSELS is increased, and the excito-motor nerves of the heart are abnormally stimulated by impulses coming from the brain. The number of heart-beats approaches the possible maximum, and the arterial pressure is increased. If a further dose of atropine is given, the vaso-motor centre no longer responds when stimulated. The small vessels are everywhere visible, the motor nerves of the heart become paralysed, and the cardiac muscle is affected at the same time. Consequently the radial pulse becomes weak, irregular, and scarcely perceptible, and there is considerable fall of the blood-pressure.

With regard to the specific action of atropine upon the smooth muscular fibres, apart from its action upon their nerves, I must refer you to the various publications on that subject.[1]

Let us now consider how these properties of atropine may be employed in therapeutics.

The drug is chiefly used in diseases of the eye. Besides dilating the pupil and paralysing the power of accommodation,

[1] Szpilmann und Luchsinger, "Atropin und glatte Muskelfaser," 'Arch. f. d. ges. Physiol.,' 1881, Bd. xxvi, s. 459; v. Bezold, 'Untersuch. a. d. physiol Laboratorium in Würzburg,' 1867, Bd. i, s. 65.

it lessens pain in the endings of the trigeminus in the cornea when they are inflamed,[1] but it does not diminish the sensitiveness of the healthy eye. Nor must we disregard its inhibitory power on the amœboid movements of the colourless blood-corpuscles during their transformation into pus cells, a point I have already demonstrated when discussing another alkaloid, namely, quinine.[2]

Atropine does not produce mydriasis when applied as an ointment to the skin of the forehead. When mydriasis occurs, it is due to the fact that a small quantity of the ointment, whilst being rubbed into the skin, has come in contact with the conjunctiva.

In bronchitis with abundant secretion, atropine checks the latter, and thus lessens the irritating cough and the asthma arising from the impeded access of air. It has been tried in cases of ptyalism due to nervous disorders,[3] and in the profuse sweats of phthisis. In the former it was injected below the submaxillary gland (Ebstein) in doses of 0·001 gramme ($\frac{1}{66}$ of a grain), and in the latter it was given in doses up to 0·002 gramme ($\frac{1}{33}$ of a grain) either subcutaneously or by the mouth. Under its use obstinate urticaria has been cured (Fraentzel), and the secretion of milk has also been checked (S. Ringer and others).

Habitual and obstinate constipation sometimes yields to small doses of atropine. This is the case when the inhibitory power of the intestines is in a hypersensitive condition. The diagnosis of such a condition is, however, unquestionably dependent upon the effect produced by the remedy. Neuralgia and spasms of the stomach, the sphincter ani, bladder, uterus, &c., may be relieved by atropine or extract of belladonna. Atropine has been found useful in epilepsy, but this mode of treatment is simply empirical—that is to say, we cannot give any explanation of the way in which the remedy acts. In cases in which such remedies as the bromides, with dietetic and general regulations, have proved of no avail, it may be worth while to try atropine. Moreover

[1] Hirschberg, in Eulenburg's 'Real-Encyklopädie d. ges. Heilkunde,' 1885, Bd. ii, s. 203.

[2] A. Zeller, 'Arch. f. path. Anat.,' 1876, Bd. lxvi, s. 384.

[3] O. Hebold, 'Zeitschr. f. Psychiatrie,' 1886, Bd. xlii, s. 432.

this action has been tested experimentally.[1] Guinea-pigs were rendered epileptic according to Brown-Séquard's method; if, however, 1—2 mg. of atropine were administered to an animal before the operation, epilepsy was not developed; further, in those animals which had been rendered epileptic, the attacks were stopped in two to three weeks by the administration of atropine. The author obtained good results[2] by giving to patients daily doses of 0·001 gramme ($\frac{1}{66}$ of a grain). Further experience may possibly teach us how to reconcile this with the fact that the cerebrum of monkeys and dogs becomes MORE SENSITIVE to stimulation after the administration of atropine.[3] It must be borne in mind that epilepsy in the human subject is dependent upon various forms of organic disease. But our knowledge of these disorders is so full of gaps that we are unable to lay down any definite rules with regard to special cases or their treatment.

The power which atropine possesses of temporarily lessening the irritability of the nerve-endings of the vagus in the heart, is beneficially employed in cases of EXHAUSTION great enough to endanger life, and especially when this condition is due to a narcotic poison.

This has been already pointed out in connection with the poisonous action of morphine (p. 94). The tracing there given, shows very well the immediate increase of the blood-pressure which follows the injection of atropine in a dog poisoned by morphine. Other experiments gave very similar results, and further most distinctly confirmed the statement of previous authors that atropine stimulates the respiratory centres in the medulla oblongata. The following is one instance out of many.

A cannula was placed in the trachea of a young dog weighing 2650 grms., to which a single subcutaneous injection of 0·2 grm. morphine had previously been given. The end of

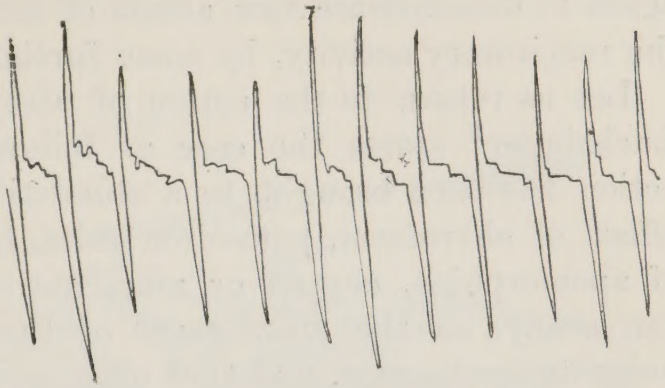
[1] Svetlin, "Atropin und seine Verwendung in der Epilepsie." Aus der Klinik von Prof. Leidesdorf in Wien. Ref. im 'Centralbl. f. d. med. W.,' 1878, s. 282.

[2] Köllner (Saargemünd) says that as a palliative in incurable epilepsy, atropine is not inferior to potassium bromide, 'Zeitschr. f. Psychiatrie,' 1882, Bd. xxxviii, s. 303.

[3] Albertoni, 'Arch. f. exper. Path. u. Pharm.,' 1882, Bd. xv, s. 248.

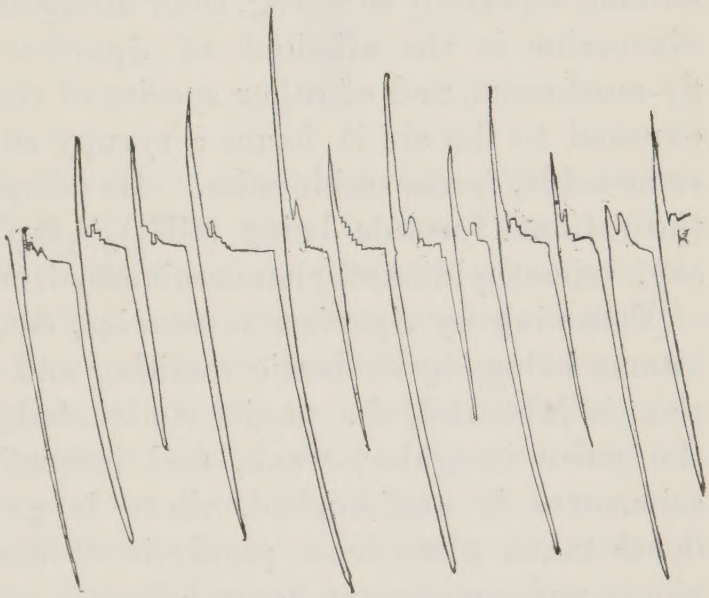
the cannula was connected, as you see here, with the smoked surface of a revolving cylinder. The respiratory movements were very slow, and gave the following tracing on the cylinder (Fig. 8).

FIG. 8.



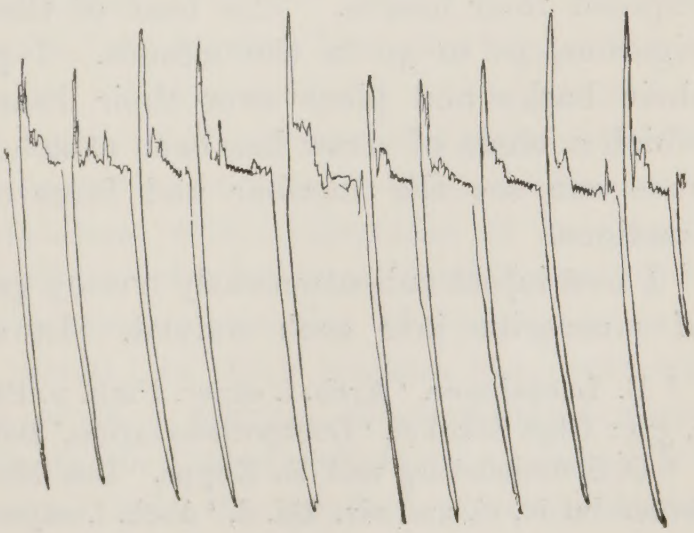
Fifteen minutes after the subcutaneous injection of 0·002 grm. of atropine, the extent of the largest oscillation was increased from 34 mm. to 54 mm., and of the others in a corresponding degree (Fig. 9).

FIG. 9.



Three quarters of an hour later the largest oscillation only extended to 47 mm., as you see from the accompanying tracing (Fig. 10). This clearly shows that the former increase was not simply due to the fact that the depression caused by the morphine was passing off, but really to the

FIG. 10.



stimulating effect of the atropine. Later on I shall have again to demonstrate this action of atropine in stimulating the respiratory activity, by some further experiments.

Let us return to the action of atropine upon the heart. Luchsinger[1] states the case as follows:—"If the heart's action has been brought to a standstill, whether from the effect of choroform, potassium salts, bile salts, oxalates, or of apomorphine, copper or zinc, antimony or quinine," we can always at the FIRST STAGE of the paralysis, cause the heart to beat again, and that often powerfully, by administering atropine.

When atropine and muscarine are alternately given to an animal, especially to a frog, their antagonism is clearly shown. Muscarine is the alkaloid of *Agaricus muscarius*, the red fly-mushroom, and of other species of the Agaricus.[2] When exposed to the air it forms a syrupy substance, which, with some acids, forms stable salts. Its composition is $C_5H_{15}NO_3$, the rational formula being $(CH_3)_3C_2H_5O_2.N.OH$—that is to say, trimethyldioxethylammoniumhydroxide.

Poisoning by *Agaricus muscarius*, &c., is accompanied in human beings by choleraic vomiting and diarrhœa. Respiration is laboured, the pupils contracted, the face cyanosed, the pulse irregular, weak, and intermittent; though consciousness is undisturbed, there is great exhaustion, and death takes place from paralysis of the respiratory movements and consequent heart failure.

Here are two frogs which have been paralysed by a small dose of curare. I have removed the sternum of each, and exposed their hearts. The beat of these in both cases is vigorous, 40 to 50 in the minute. I put the animals on their backs and place over their hearts a light lever to which a blade of straw has been attached, so that my audience can see the number and force of the cardiac contractions.

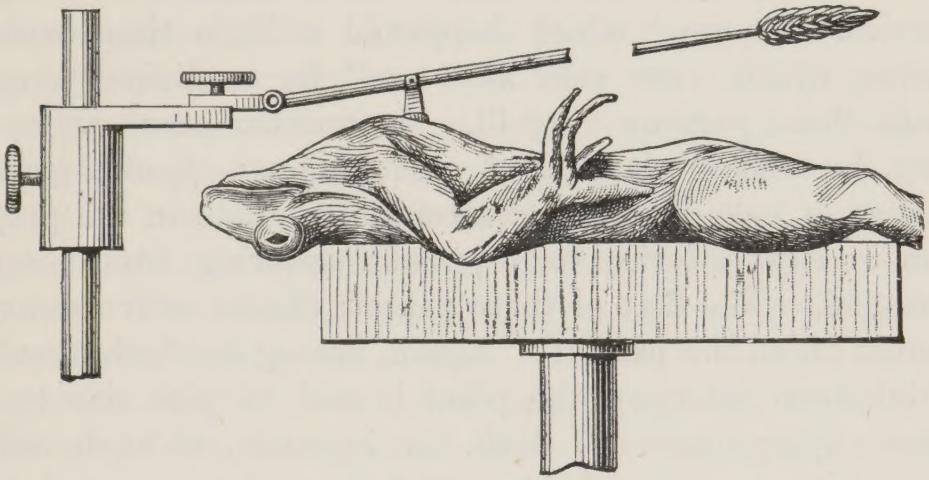
I now inject subcutaneously 0·0005 grm. of hydrochloride of muscarine into each animal. In a few minutes the

[1] B. Luchsinger, 'Arch. f. exper. Path. u. Pharmak.,' 1881, Bd. xiv, s. 374; Olga Sokoloff, 'Doctordissertation,' Bern, 1881.

[2] O. Schmiedeberg und R. Koppe, 'Das Muscarin,' Leipzig, 1863; ferner im iv, vi, und xiv, Bd. d, 'Arch. f. exper. Pathol. u. Pharmak.'

heart gradually ceases to beat. The auricles are the only parts which show any movement, the ventricle being inflated like a balloon.

FIG. 11.



This stoppage of the heart may last for several hours, but even at the end of that time I should be able to show the experiment I am about to perform on one of the animals. I inject 0·0005 grm. atropine sulphate under the skin of the thigh. The LYMPH-HEARTS still pulsate, and consequently the atropine is driven on, notwithstanding the cessation of the circulation of the blood. In less than two minutes you see that the lever on this frog begins to move, at first feebly and with intervals of a few seconds, but soon strongly and frequently; at the end of four minutes the heart-beats are normal, both with regard to their number and strength, the heart of the other frog meanwhile remaining quite motionless.

This curative action of atropine has also been tried in warm-blooded animals. A dog received 0·011 gramme of muscarine. In the course of six minutes the pulse fell from 100 to less than 10, respiration became feeble and infrequent; the animal lay motionless, with contraction of its pupils, profuse salivation, and muscular tremors; death seemed to be impending. A subcutaneous injection of 0·002 gramme of atropine was now given; in four minutes the heart was beating at the rate of 96 a minute, the respiratory movements improved, the pupils dilated, salivation ceased, and in a few hours the animal, with the gradual re-establishment

of its respiration—which certainly took the longest time to return to its normal condition—became quite lively (Schmiedeberg).

Cases of poisoning by atropine are pretty frequent. I have already referred to some which were due to eating the berries. In one[1] which happened a little time back, the leaves, which were sold as "tea" for medicinal purposes, made three persons very ill. In another case[2] an apothecary, by mistake, instead of 0·06 gramme ($\frac{9}{10}$ of a grain) of extract of belladonna used atropine sulphate in the preparation of suppositories for a patient suffering from fissure of the anus. The first of these caused violent convulsions, and almost killed the patient. Again, eating the flesh of animals which have fed upon the plant is said to give rise to dangerous symptoms—the flesh, for instance, of such animals as rabbits, hares, or birds, which have been proved to be nearly immune to atropine. According to Bouchardat, the vineyard snail is also immune. A case related by Schauenstein (loc. cit., p. 653) is instructive as illustrating the ways in which atropine poisoning may arise.

A young and healthy man was seized with very clear symptoms of atropine poisoning without being able to say in the least how he had taken the poison. His illness commenced soon after taking some coffee. It was then discovered that the cook, in straining the coffee, had used a linen rag which a lodger, some time before, had dipped in an atropine solution, and employed as a compress over his eyes. The rag had been thrown away unwashed, and in this state had been used by the cook for domestic purposes.

The physician in this case formed a correct diagnosis in spite of the apparent absence of the *corpus delicti*. A less successful result followed in eight cases of poisoning by atropine at Geneva in 1868, caused by a hospital nurse who was the subject of monomania. This woman, under the pretext that she was suffering from disease of her eyes, procured a variety of physicians' prescriptions, and by getting them

[1] Morel, "Trois Cas d'Empoisonnement par la Belladonne," 'Ann. de la Soc. de Méd.,' Gent, 1873.

[2] Schüler, "Atropinvergiftung, durch Morphin subcut. geheilt.," 'Berl. klin. Woch.,' 1880, s. 658.

illegally dispensed a second time, obtained possession of a large number of bottles of atropine solution. She then indulged in the amusement of endeavouring to poison the residents in the hospital and the patients under her charge, and even the families of the latter. Six of those to whom poison was given, died. Probably the number of deaths was greater, but six only could be clearly proved. The physicians first called in regarded these cases of atropine poisoning as fever, encephalitis, congestion of the brain, commencing insanity, and mania. At last a doctor who was consulted recognised the characteristic symptoms, and made a correct diagnosis. The whole matter was then soon cleared up and the murderess imprisoned.[1]

Slight forms of poisoning frequently occur, in cases of eye disease, from the repeated application of atropine solutions to the conjunctiva and from the solution passing into the throat and elsewhere through the nasal ducts. "I felt as though I were mad; a terrible sensation of insecurity and dread came over me, I could not retain my ideas; I did not know whether I was dreaming or awake, whether the horrid visions before me were real or phantasies." This was the description of his feelings given by a friend of mine who was suffering from an affection of his eyes.

Some people are extremely sensitive to very small doses of atropine; others, even if a perfectly blameless preparation is dropped into the eyes, suffer from catarrhal inflammation of the conjunctiva; elderly people are sometimes attacked by such violent tenesmus, together with retention of urine, from the absorption of atropine dropped into the eye, that the treatment has to be discontinued (v. Wecker). Children are said to tolerate the drug better than adults.

The DIAGNOSIS of atropine poisoning is not difficult in most cases, for the dilatation of the pupils soon directs attention to the other symptoms, some of which are very marked. At the same time we must remember that atropine when given internally does not, as a rule, cause such immediate and considerable mydriasis as is set up when the drug is dropped into the eye; further, according to several authorities, the dilatation of the pupils in CHILDREN is altogether less marked.

[1] 'Procès criminal contre Marie Jeanneret,' Lausanne, 1869.

Other inflammatory conditions of the head are not accompanied by dryness of the mouth or redness of the throat, rapid breathing, &c. The inflammatory swelling of the tonsils associated with other febrile symptoms, such as restlessness, heat of the head, quick pulse, rapid respiration, and also the commencement of scarlet fever, are accompanied by a considerable rise of temperature in the rectum; but in poisoning by atropine there is very little if any rise of temperature.

Vomiting of undigested berries of a black colour is mentioned in several cases, as being among the earlier symptoms of poisoning. If the berries are recognised by the physician the diagnosis is easily made. In a case described by Taylor the seeds of the plant were found in the evacuations after the administration of purgatives. They are oblong, obtusely three-cornered, or reniform, with a brownish-black, somewhat rough surface, and about 2 to 3 mm. (about $\frac{1}{15}$ to $\frac{1}{12}$ of an inch) in length.

The urine of people poisoned by atropine has been dropped into the eye of a cat, with the result that mydriasis was soon induced. This proceeding is facilitated by evaporating the urine to a small quantity. In order to try how quickly the same result could be attained by a more reliable method, I made the following experiment:

I added 1 mg. ($\frac{1}{66}$ of a grain) of sulphate of atropine to 250 c.c. (about eight ounces) of urine, evaporated it to about 25 c.c. (about six drachms), and added a few drops of ammonia and 25 c.c. of chloroform, shaking the whole together. I then poured it into a separator, drew off the chloroform, and evaporated it over a water-bath. A very slight residue was left, which I dissolved, by rubbing it with a glass rod, in about 1 c.c. (fifteen drops) of warm acidulated water, and then dropped it into the eye of a cat. The whole proceeding, beginning with the evaporation of the urine, took about forty-five minutes.

The eyes of the cat distinctly differed in appearance an hour after this solution had been applied. The pupil of the one not interfered with was very narrow, whilst the pupil of the other was 4 mm. (about $\frac{1}{6}$ of an inch) wide.

In the TREATMENT of poisoning by atropine, we must first

of all endeavour to eliminate the poison from the intestinal canal, or to combine with it some substance that will render it innocuous. Tannic acid is not very trustworthy; the salts of atropine are, it is true, precipitated by it, but the precipitate is dissolved in hydrochloric acid. Garrod, from his experience in two cases, recommends the administration of animal charcoal. The property this substance possesses of so absorbing the alkaloids as to render their extraction by water difficult, is well known to chemists. For this reason, and on account of the fact that it is innocuous, animal charcoal may be administered in order to impede the absorption of any atropine which may still remain in the stomach.

MORPHINE is an important antidote in atropine poisoning. Its administration for this purpose is of ancient date. As far back as 1661, Horst described a case in which a man poisoned by atropine had been cured by the administration of theriacum, an electuary containing opium. From that date up to our own time recourse has often been had to this mode of treatment. In recent times the point has been investigated by experiments on animals, and at the present day the state of our knowledge is as follows.

It has been shown in a great number of instances that in atropine poisoning the CEREBRAL EXCITEMENT can be removed, or at any rate greatly diminished, by a large dose of morphine. In addition to the cases previously[1] reported by me, I will here refer to one of many which have since been published.[2]

Four children, from three to seven years of age, eat the seeds of *Datura stramonium*, the alkaloid of which is isomeric and in some degree identical with atropine. The symptoms of poisoning in three of the patients were severe, but did not indicate danger to life. In the fourth, however, a boy of five, the case was different. The pulse was very frequent, small, and thread-like. The child was seized with continuous clonic convulsions of such violence that its body was tossed about the bed. Respiration, and gradually the pulse also,

[1] C. Binz, "Intoxicationen des Kindesalters," in 'Gerhardt's Handbuch,' 1877, Bd. iii, ss. 408 und 420; an instructive case reported by L. Kugler, 'Arch. f. Ophthalmologie,' 1870, Bd. xvi, s. 345.

[2] C. Strömberg, 'Petersburger med. Wochenschr.,' 1879, s. 429.

became most irregular. Death seemed inevitable. As a "last resource" morphine was administered; 0·02 gramme ($\frac{3}{10}$ of a grain) divided into three doses was injected subcutaneously within an hour. AFTER THE FIRST INJECTION THERE WAS A CHANGE FOR THE BETTER; the pulse became stronger and less frequent; respiration soon improved; from time to time the convulsions intermitted, the intervals growing longer and longer; and two hours afterwards the child was out of danger. The restlessness, it is true, continued some hours before sleep set in, but this gave rise to no anxiety. "Even if it is asserted," remarks the author, "that the case might have ended in a similar way supposing that morphine had not been given—which I for my part do not believe—the facts reported, nevertheless, clearly point to the existence of an antagonism between morphine and daturine. The correctness of this conclusion is confirmed by the fact that although the doses of morphine were very large for a child of that age, they did not produce sleep."

This tolerance of large doses of morphine without any of the usual effects being developed, almost invariably shows itself in patients who are under the influence of atropine. In the case previously mentioned, where poisonous symptoms were developed after using a suppository, 0·06 gramme ($\frac{9}{10}$ of a grain) of morphine was given at first to the patient, who was then suffering from general convulsions; an hour later 0·03 gramme (nearly $\frac{1}{2}$ a grain) was injected, so that NINE TIMES the ordinary soporific dose was given. After the first dose the convulsions were less frequent, and five hours later the patient could get out of bed to pass urine, was able to speak connectedly, and only complained of impaired vision and of dryness in the throat. He now for the first time fell into a deep and sound sleep. Three days afterwards he went back to his ordinary business. The mydriasis lasted eight days longer, proving that the effect of the atropine had been very considerable.

It has been shown in my laboratory that the nervous excitement and convulsions caused by atropine in young dogs cease when moderate quantities of morphine are injected.[1] Animals of a lower order than the dog are useless, here, for

[1] Heubach, 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. viii, s. 31.

experimental purposes, on account of their immunity to atropine; certain statements denying the antagonism of the drugs are partly due to the use of these animals in the experiments. Even the dog is much less affected by atropine than human beings, whilst morphine is not such an efficient antidote. This animal only serves to give a general illustration of the action of the remedy, and to show its stimulating effect upon the heart and respiration; the effect of morphine and similar drugs in subduing the cerebral excitement due to atropine is much more marked in human beings. Moreover it is only in badly devised experiments that the ANTAGONISTIC ACTION of these two alkaloids has not been observed.[1]

When I narcotised some healthy rabbits by injecting 0·02—0·06 gramme of morphine into the jugular vein, the frequency of respiration as measured by the pneumatograph was almost immediately diminished to one third and less, of its normal rate (see page 53). I then injected 0·002—0·04 gramme of atropine. Very shortly afterwards the respiratory movements were increased to the extent of 45, 50, 60, 45, and 25 per cent., in two instances even to the extent of 100 and 133 per cent.; and, further, they continued to be more rapid than they were before the administration of atropine.[2]

A second observation of great importance from a therapeutic point of view was made at the same time; namely, that atropine increased the general SENSITIVENESS of the animals. I have described this before, but never in detail. One of the experiments was as follows:—The cornea and nose of a healthy animal were stimulated with a faradic current; the volume of air respired showed an increase from 170 to 270, 230, 280, 200, 320, and 250 c.c. in half a minute. The same stimulation did not produce the slightest change when the animal was previously narcotised by morphine. Atropine was then administered to the narcotised animal, and after sufficient time had elapsed for the effect of this drug on the respiration to subside, so that the volume of air

[1] H. Heubach, 'Berl. klin. Wochenschr.,' 1878, s. 767. See also Vollmer and Levison, note, p. 222.

[2] C. Binz, 'Deutsch. med. Wochenschrift,' 1887, s. 21; und 'Archiv f. klin. Med.,' 1887, Bd. xli, s. 174.

respired was only 60 c.c., it was found that the sensibility of the reflex organs, and consequently the possibility of improving the respiration by external stimulation was such, that on applying the current the volume of air respired was increased at once to 100, 70, 80, and 90 c.c. in half a minute.[1]

Thus we see that in animals narcotised by morphine the administration of atropine quickly raises the blood-pressure, greatly amplifies the decreased respiratory movements, and restores the general reflex excitability, even though it may have been almost totally abolished. The improvement in the reflex excitability is of practical importance; it teaches us that the application of external irritants, such as mustard plasters, rubbing the skin, electricity, ammonia, &c., which are generally used in these cases, can probably only act upon the nervous centres, when the injection of atropine has rendered them capable of responding to stimulation.

As might have been expected, this therapeutic antagonism is not confined to atropine and morphine alone. In cases of poisoning by CHLORAL and similar drugs the impaired action of the heart and enfeebled respiration will also be improved by atropine; whilst, on the other hand, the increased sensitiveness of the nerve-centres produced by atropine may be lessened by chloroform. All this is confirmed by some careful observations taken in a number of cases of poisoning by atropine, which have been lately published.

The antagonism between atropine and morphine is very plainly shown by the administration of the latter drug to patients who are very sensitive to its action, and in whom violent vomiting is induced even after small doses. In anæmic individuals this is one of the first effects produced

[1] The much-discussed question as to the therapeutic antagonism between morphine and atropine has, recently, been again thoroughly investigated, and has been answered most conclusively in the affirmative. Reference may be made to the two series of experiments carried out in my laboratory; E. Vollmer, 'Arch. f. exper. Path. u. Pharmak.,' 1892, Bd. xxx, s. 385, and A. Levison, 'Berl. klin. Wochenschr.,' 1894, No. 39; also C. Binz, 'Centralbl. f. klin. Med.,' 1893, No. 2, and J. Samelsohn, ibid., No. 11; H. Wood and Cerna, 'Journ. of Physiol.,' 1892, Dec. suppl., p. 880; E. Stadelmann, 'Zeitsch. f. klin. Med.,' 1894, Bd. xxvi, s. 267.

by morphine. One, or often only half a centigramme is sufficient to stimulate the "vomiting centre" in the medulla oblongata; and this is still more marked when the remedy is employed in diseases which are usually accompanied by vomiting—such, for instance, as the different forms of peritonitis, in which the use of morphine is so urgently required in order to lessen the pain. Some individuals, moreover, are subject after every injection of morphine to certain other effects, such as a feeling of languor, mental depression, or inability to move. The addition of a little atropine,[1] 0·0005 gramme ($\frac{1}{130}$ of a grain) to 0·01 gramme ($\frac{1}{6}$ of a grain) of morphine, has been recommended in order to obviate such unpleasant results. The full anodyne effect of morphine is then produced, and the patient is not afterwards troubled with these most distressing symptoms. This has been confirmed by other observers. In the works referred to below[2] twenty cases of this particular kind are reported.

Whether or not the difference in the effects of the drugs to which reference has been made, can be included in the term antagonism is a point which has been warmly discussed, but it is not of the slightest importance. Anyone who considers the word unsuitable can discard it.

The largest single dose of atropine sulphate is 0·001 gramme ($\frac{1}{66}$ of a grain); the largest quantity to be given in one day is 0·003 gramme ($\frac{1}{22}$ of a grain). In cases of morphine poisoning as much as ten times the ordinary dose has been given, and, as experience shows, this is not followed by any injurious effects when it is administered under suitable conditions. In an adult you administer first $\frac{1}{60}$ of a grain, and then cautiously increase the dose, watching its effect.

Extractum Belladonnæ, the alcoholic extract made from the fresh leaves of belladonna in its flowering stage, is still officinal. It is a thick brown mass, which forms an almost clear solution with water. The quantity of atropine contained in it naturally varies, and its action is therefore un-

[1] Frickenhaus, 'Allg. med. Centr. Zeitung,' Berlin, 1875, s. 1061.

[2] Lagoda, 'St. Petersburger med. Wochenschr.,' 1877, s. 98; Claus, 'Allg. Zeitschrift f. Psychiatrie,' 1877, Bd. xxiii, s. 529; P. Kowalewsky, "Eine Atropin-Psychose.," 'Zeitschr. f. Psychiatrie,' 1880, Bd. xxxvi, s. 431 (improvement and recovery through the use of morphine).

reliable. Its maximum single dose is 0·05 gramme (¾ of a grain) ; the maximum dose in a day is 0·2 gramme (3 grains).

Datura stramonium, thorn-apple, and *Hyoscyamus niger*, henbane, two indigenous plants belonging to the Natural Order Solanaceæ, are allied to *Atropa belladonna*. The leaves of the first, and the leaves and flowering branches of the second are officinal. Both have long been known as poisonous and medicinal plants, the properties of which are closely allied to those of *Atropa belladonna*, but it is only recently that we have obtained a clear insight into the nature of the essential constituents of these drugs.

Daturine is not a simple alkaloid, but consists of varying quantities of atropine and hyoscyamine. This latter, the alkaloid of henbane, is isomeric with atropine. When treated with baryta or hydrochloric acid it absorbs one molecule of water, and is, like atropine, resolved into the two compounds, tropine, $C_8H_{15}NO$, and tropic acid, $C_9H_{10}O_3$, but it differs from atropine in crystallising less readily, as well as in its solubility, and its behaviour with other reagents.[1] It has long been known that two alkaloids, differing in their chemical properties, could be obtained from the datura ; as, however, they produced apparently similar effects, they were termed heavy and light atropine.

According to more recent investigations,[2] a good specimen of belladonna root is said to contain no atropine whatever, but merely hyoscyamine, which is changed into atropine only after prolonged heating, or by treatment with alkalies, &c.

Duboisine, from *Duboisia myroporoides*, an Australian shrub, is, according to Ladenburg, merely hyoscyamine.

Stramonium leaves are used in asthma ; they are smoked in two ways ; they either form the outside covering of cigars, or are mixed with some good light tobacco. It is still uncertain whether the effect is due to the two alkaloids or to combustion products. The results obtained from the use of this remedy have, however, in many cases been so favorable that patients highly appreciate both the

[1] A. Ladenburg, 'Ann. d. Chemie,' 1880, Bd. ccvi, s. 274 ; E. Schmidt, ibid., 1881, Bd. ccviii, s. 196.

[2] M. Will, 'Ber. d. deutschen chem. Ges., 1888, Bd. xxi, ss. 1723 und 2777.

remedy and the method of using it. The preparations of henbane, especially the alcoholic extract, were formerly largely employed in neuralgia, and also in severe coughs.

HYOSCYAMINE, which crystallises in small needles, is a powerful mydriatic, and on this account is used in ophthalmic practice. It differs from atropine in producing a soporific effect, and it is said to have been found useful in insanity in doses of 0·002—0·005 gramme ($\frac{1}{33}$ to $\frac{1}{14}$ of a grain), which may be given a few times during the day. It is not officinal.

The seeds of henbane contain, in addition to hyoscyamine, HYOSCINE, an isomer of atropine which crystallises readily in combination with hydrobromic or hydriodic acid. These compounds have been successfully administered in asthma and various forms of nervous excitement. As is usually the case, the medicinal use of this remedy preceded any investigation of its physiological properties by experiments on animals.[1] Omitting toxicological details, I will merely refer to the following effects of the drug.

Hyoscine does not act on the cerebral cortex of animals, and only slightly on that of healthy people, whilst in cases of insanity it is a powerful sedative. In other respects its action resembles that of atropine.[2] It is said sometimes to accelerate and sometimes to diminish the action of the heart. Most probably this is due to individual idiosyncrasies. It appears in the urine unchanged, or at any rate as a substance which has the same action.

The favorable results which have often been attributed to the use of hyoscine in cases of insanity and similar diseases, are disputed. Possibly the failures may be due to the use of a faulty or impure preparation, as is almost invariably the case when a new medicine is introduced.

Fraentzel and others recommend the use of hyoscine in the night sweats of phthisis when atropine is, or has become, ineffective. He gave 0·0005 gramme ($\frac{1}{100}$ of a grain) of iodate of hyoscine subcutaneously or

[1] Edlefsen and Claussen, the 'Doctordissertation' of the latter, Kiel, 1883; Kobert, 'Arch. f. experim. Path. u. Pharmakol.,' 1887, Bd. xxii, s. 396; Erb, 'Therap. Monatshefte,' 1887, s. 252.

[2] Peters (Bonn), 'Deutsch. med. Wochenschr.,' 1894, s. 263.

internally.[1] Sometimes, however, narcosis and collapse followed its use.

Until recently hyoscine hydrobromate was officinal, but when it was discovered that the hyoscine of commerce consisted chiefly of scopolamine the name was altered, and it is now termed SCOPOLAMINUM HYDROBROMICUM, scopolamine hydrobromide: the formula for this alkaloid is $C_{17}H_{21}NO_4$. It is obtained from the root of *Scopolia atropoides*, which belongs to the Solanaceæ, and is grown in Central Europe. Its hydrobromate consists of rather large colourless crystals, which are easily soluble in water and alcohol, and have a bitter and harsh taste, and a slightly acid reaction. It is injected subcutaneously in carefully measured doses of 0·0002 to 0·0005 gramme ($\frac{1}{330}$ to $\frac{1}{130}$ of a grain); when any larger dose is prescribed it must be marked thus (!), to indicate that such a dose is specially ordered. At first only a single dose of 0·0001 gramme ($\frac{1}{660}$ grain) should be given subcutaneously.

Atropine when dissolved in strong hydrochloric acid takes up water, and is resolved into tropine and tropic acid:

$$C_{17}H_{23}NO_3 + H_2O = C_8H_{15}NO + C_6H_5.CH.(CH_2OH).COOH.$$

These two substances, gently heated together with dilute hydrochloric acid, are reconverted into the alkaloid, atropine.

If in this reconversion we use, instead of tropic acid, its analogue, mandelic or phenyl-glycolic acid, $C_6H_5.CH.OH.COOH$, we obtain a body resembling atropine, which is called HOMATROPINE. Its composition is $C_{16}H_{21}NO_3$.[2]

Homatropine is officinal as HOMATROPINUM HYDROBROMICUM, hydrobromate of homatropine. It is a white, odourless, crystalline powder, readily dissolves in water, and has a neutral reaction. The action of this derivative of atropine is very similar to that of the latter body, but weaker and more transitory.[3] This is the reason why homatropine is

[1] Fraentzel, 'Charité-Annalen,' 1883, s. 301; Petersen und Langdon, ref. 'Centralbl. f. klin. Med.,' 1886, s. 389; for a summary of the question see S. Rabow; 'Therapeutische Monatshefte,' 1889, s. 367; "Vergiftung durch Hyoscin," Adler, 'Berl. klin. Wochenschr.,' 1891, No. 10.

[2] Ladenburg, 'Ann. d. Chemie,' 1880, Bd. ccxvii, s. 82.

[3] Tweedy and Sydney Ringer, 'Lancet,' 1880, vol. i, p. 795; Bertheau, 'Berl. klin. Wochenschr.,' 1880, No. 41.

used in ophthalmic surgery, especially in those cases where it is necessary to dilate the pupil for diagnostic purposes. Its local anodyne effect is said to be much greater than that of atropine.[1]

The maximum dose and the maximum quantity to be administered internally during the day, are the same as those of atropine.

The following formulæ express clearly the relationship between homatropine and atropine:

$$\underset{\text{Atropine.}}{C_{17}H_{23}NO_3} + \underset{\text{Water.}}{H_2O} = \underset{\text{Tropic acid.}}{C_9H_{10}O_3} + \underset{\text{Tropine.}}{C_8H_{15}NO}.$$

$$\underset{\text{Tropine.}}{C_8H_{15}NO} + \underset{\text{Mandelic acid.}}{C_8H_8O_3} = \underset{\text{Water.}}{H_2O} + \underset{\text{Homatropine.}}{C_{16}H_{21}NO_3}.$$

Mandelic or phenyl-glycolic acid possesses no other medicinal interest. It is formed by heating amygdaline, a crystalline body existing in bitter almonds, with hydrochloric acid, and it crystallises in shining prisms or plates, which are easily soluble in water.

[1] Filehne, 'Berl. klin. Wochenschr.,' 1887, No. 7.

XI.

Caffeine—Whence obtained—Chemical characters—Action on human beings in full doses—Investigation of its action on animals—Increases the temperature, blood-pressure, and respiration—Stimulates the reflex excitability and the cerebral function—Diuretic action—Soluble double salts—Theobromine, a powerful diuretic—Coffee and tea—Guarana—Cola nut—Coca—Digitalis purpurea—Action on the frog's heart—On the pulse, blood-pressure, and temperature of warm-blooded animals—Administration in heart disease and dropsy—Cumulative action—Preparations—Poisonous effects of digitalis—Analogous drugs and preparations—Strophanthus.

CAFFEINE in some measure resembles atropine in its physiological action and its therapeutic uses.

It is obtained from different plants, which I will describe later on. It derives its name from *Coffea arabica*, the coffee tree, from the seeds of which it was first obtained by Runge in 1820. Several years later THEINE was discovered in the leaves of Chinese tea, and in 1838 C. Jobst showed that the two substances are chemically identical.

Caffeine occurs in white, silky, feathery, needle-like crystals, and forms, when dissolved in eighty parts of water, a neutral solution with a slightly bitter taste. In double its weight of boiling water it forms a solution which solidifies as a crystalline mass on cooling. It dissolves in fifty parts of alcohol, in nine parts of chloroform, but only to a slight extent in ether. When it is free from moisture, and is carefully heated up to 180° C., it sublimes without undergoing decomposition or leaving any residue. If we evaporate a solution of caffeine in chlorine water on the water-bath we obtain a reddish residue, which becomes purple when

moistened with a solution of ammonia. Tannic acid precipitates caffeine from an aqueous solution, but redissolves the precipitate if added in excess. Its empirical formula is $C_8H_{10}N_4O_2+H_2O$, and it is related to uric acid, the formula for which is $C_5H_4N_4O_3$. Caffeine is derived from xanthine, $C_5H_4N_4O_2$, by substituting three molecules of methyl for three atoms of hydrogen, thus forming $C_5H(CH_3)_3N_4O_2$, trimethylxanthine or caffeine. This relationship with uric acid explains the development of the purple colour above mentioned—a reaction which can also be obtained from uric acid in a similar way, and is then called the murexide reaction.

Caffeine is ranked with the vegetable alkaloids, but possesses only feeble basic properties. Its salts are unstable, and are decomposed by water; none of them therefore have as yet been included in the German Pharmacopœia. If caffeine is heated with strong caustic potash it is converted, with evolution of carbonic acid, into a true base, namely, caffeidine, $C_7H_{12}N_4O$.

The effect of caffeine on the human subject has been studied in various ways, experimentally and otherwise. The following statements may be selected as being the most instructive.

Frerichs took 1·5 grammes (23 grains) of caffeine in one dose; fifteen minutes afterwards his pulse became full and hard, whilst its rate rose from 70 to 80; there was a sense of heaviness and oppression in his head, with buzzing in the ears, giddiness, and violent throbbing of the arteries; he also became extremely restless and excited. This condition lasted for an hour, when the severity of the symptoms gradually diminished. A similar effect was observed in the students of C. G. Lehmann, who took 0·3—0·6 gramme ($4\frac{1}{2}$—9 grains). Aubert took 0·5 gramme ($7\frac{1}{2}$ grains), and a quarter of an hour afterwards his pulse was slightly accelerated; later on his head became affected and his hands trembled: these symptoms, however, soon passed off.

A slightly built woman, aged thirty years, was given 0·24 gramme ($3\frac{1}{2}$ grains) of caffeine twice daily. After taking the first powder she felt giddy and languid. Great precordial distress supervened, with PALPITATION, VERY FREQUENT

PULSE, PULSATION OF THE ABDOMINAL AORTA, trembling of the limbs, grinding of the teeth, and a feeling of spasmodic constriction of the throat and neck. This condition lasted for three hours, but improved gradually, and in twenty-four hours entirely disappeared. This marked effect of two doses, of 0·24 gramme (3½ grains) each, was due to the debilitated, anæmic, and very sensitive condition of the patient.[1]

Another woman who, a year before, after her first confinement, had been treated for anæmia, and sent into the country, was suddenly taken ill two days after she had returned home. Her periods, since their re-establishment, had always been regular though scanty. The return of the discharge was expected at the beginning of the month, but did not appear. The idea of pregnancy was so dreaded by the woman that, in order to produce abortion, she took a very strong decoction of coffee, prepared as follows:—500 grammes (about 17½ ounces) of boiling water were poured over 250 grammes (rather more than ½ lb.) of fresh, slightly roasted, and finely ground coffee, and the whole boiled for five minutes; this was then strained, and as much as possible pressed from the grains through a thick woollen filter. The woman drank off the whole of this decoction, without adding anything to it.

The first symptoms showed themselves within a quarter of an hour. The physician[2] who saw the patient two hours after she had taken the dose found her sitting up, as she declined to lie down either on the bed or the sofa. Her face was pale, and showed the utmost anxiety. She kept on moaning, complained of want of air, clung to the furniture and to the people about her, begged for help, moved restlessly on her seat, and tried to rise, but always sank back powerless. There were constant spasmodic movements of her limbs, especially of her hands, resembling those of chorea, so that she could hold nothing. She recognised the people and her surroundings, and was conscious of the cause of her illness, but nevertheless her mind was evidently not quite clear; for on the following day she had only a dim recollection of what had taken place. The respiration was laboured, short

[1] Kelp; 'In den Memorabilien von F. Betz,' 1887, s. 494.

[2] Curschmann, 'Deutsche Klinik,' 1873, s. 377.

and quick, 24 to 30 in the minute, in keeping with her complaints as to want of breath, which amounted at times to a feeling of suffocation. An examination of the lungs revealed nothing abnormal. The patient specially complained of violent palpitation. AN EXTREMELY FORCIBLE ALMOST HEAVING CARDIAC IMPULSE was felt in the normal position and over a much larger extent of the chest than usual. The heart-sounds were loud and banging, but clear. Arteries small and hard; very tense, well-marked *pulsus celer*, 112 in the minute.

Diarrhœa and a tendency to vomit set in an hour later. There were watery evacuations of the bowels almost every half-hour, and sometimes these occurred immediately one after the other; there was only slight pain in the stomach, but violent tenesmus. The patient was also tormented by a frequent desire to micturate, and was compelled to do so every quarter of an hour. THE QUANTITY OF URINE WAS GREATLY INCREASED, the specific gravity falling to 1014; the colour was bright yellow, and no foreign substance was present: caffeine was not tested for. This condition lasted until late in the evening, when under the influence of morphine she became quiet and then had a short sleep. For the rest of the night the patient was restless, and her short sleeps were broken by vivid dreams and phantasies. It was only after forty-eight hours that the symptoms of poisoning gradually passed off; menstruation afterwards came on in the usual manner.

The possible effect of some pyrrol derivative must not of course be left out of the question, but as the coffee was only slightly roasted, and the decoction was, moreover, boiled, the effect of any such derivative would be very slight in comparison with that of the caffeine. Taking an average estimate, there must have been about 1·6 grammes (24 grains) of the alkaloid in the coffee which the woman drank.

Experiments[1] upon animals give us an explanation of the

[1] C. Binz, "Beiträge zur Kenntniss der Kaffebestandteile," 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. ix, 315, with references to thirty papers of other authors; also ibid., 1891, Bd. xxviii, s. 197. J. Peretti, 'Doctordiss. a. d. Pharmak. Instit. zu Bonn,' 1875; Semmola e Marcone, 'Il Progresso Medico,' 1890, vol. iv, No. 12, *et seq.*

various symptoms produced by the caffeine in the case just related.

The stimulation of the large muscles is due to the direct action of the caffeine upon the MOTOR NERVE-CENTRES; the alkaloid also acts directly upon the MUSCULAR TISSUE. If we moisten the latter with a not too dilute solution of caffeine, it becomes hard, white, and coagulated, and loses its irritability. If we examine it with the microscope we see that the fibres are contracted, the longitudinal striæ are distinct, whilst the transverse striæ have disappeared and the sarcolemma has become detached. Evidently caffeine by itself, when given internally and diluted in the fluids of the body, could not directly irritate the tissue in such a way as to develop, in the living subject, tremors, rigidity, and convulsions. And, moreover, if we divide a motor nerve we can prevent the symptoms in the muscles supplied by that nerve; artificial respiration has the same effect.

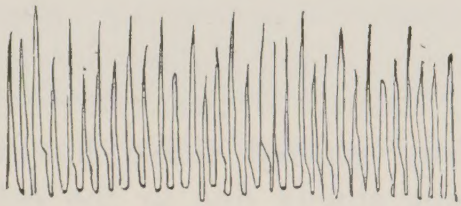
THE TEMPERATURE OF THE BODY RISES in consequence of the contraction of the muscles. Medium doses, which produce the initial symptoms of poisoning but not convulsions, cause a rise of 0·6° C. (about 1° F.); large doses which induce stiffness of the muscles and restlessness cause a rise of 1 to 1·5° C. (1·8 to 2·7° F.)—the maximum being reached in from one to two hours. The temperature gradually falls again, but remains above the normal for hours.

Increased ACTION OF THE HEART is brought about by moderate doses. I have determined this by means of a manometer, in dogs which were anæsthetised by alcohol. The blood-pressure rose, in ten minutes after a subcutaneous injection, from 84—88 to 120—128 mm. in one case, and in another from 70—90 to 125—140 mm. At the same time the pulse-rate was doubled. This increase of the blood-pressure is independent of the vagus, and takes place even when this nerve is divided. It is, of course, intelligible that poisonous doses of this substance, as of every other stimulant, can lower the blood-pressure by stopping the heart.

I have always been struck by the marked increase which took place in the RESPIRATIONS after an injection of caffeine. Thirty c.c. of absolute alcohol diluted with the same amount

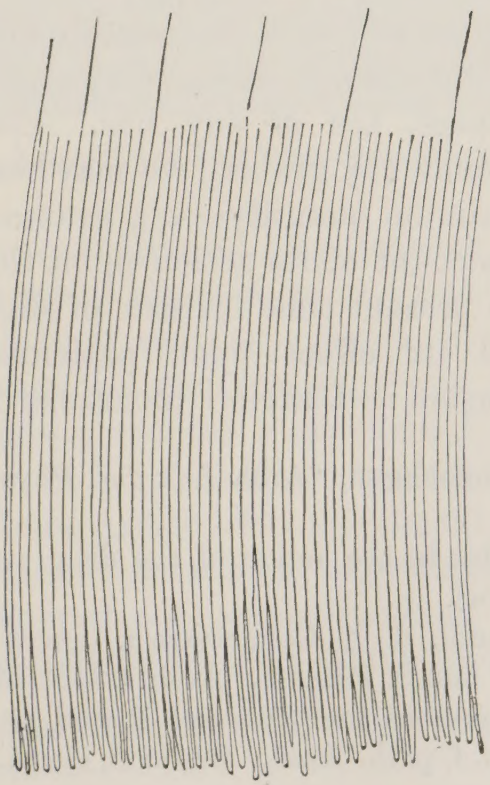
of water were given by means of an œsophageal tube to a young dog which had been without food for twenty-four hours. The animal was completely narcotised, and a Y-shaped glass tube, one limb of which was connected by a lever to the recording surface of a revolving tambour, was tied in an opening in its trachea. Here is a tracing taken with this instrument (Fig. 12), showing the very reduced rate of the respiratory rhythm.

FIG. 12.



I now inject under the skin of the animal 0·15 gramme of caffeine dissolved in 10 grammes of water. The animal during the operation appears as if it were dead, but the extent of the respiratory movements is quickly increased, and in fifteen minutes they appear as depicted on the accompanying tracing (Fig. 13).

FIG. 13.



This increase, it is true, does not last long, for in an hour the respiration is as quiet as it was at the commencement of the experiment; still the transitory improvement caused by the caffeine was very well marked. The tracing showed an increase even in fifty seconds after the injection, not only in the extent, but also in the number of the respirations.

The effect of caffeine on human beings[1] corresponds with the stimulating action which I have just demonstrated to you. As a rule, the time of reaction—that is the interval which elapses between a systematic stimulation and the muscular contraction which follows it—is shortened in a striking manner, twenty to twenty-five minutes after an infusion of slightly roasted coffee has been taken, the action of this being chiefly due to the caffeine it contains. This condition lasts for two hours. Further, the sensibility, as measured by the power of localising pressure sensations, is very materially increased a few minutes after a dose of 0·1 gramme (1½ grains) of caffeine in an infusion of 34 grammes (8½ drachms) of coffee is taken.

Caffeine was very rarely used by physicians until recently. Occasionally it was given in hemicrania or megrims, and often with good results. We are ignorant of the way in which this improvement is effected, and what we know of the pharmacological action of the remedy throws no light on the subject.[2] Only large doses, given at the commencement of the illness, are of any use. Commencing with doses of 0·1 gramme (1½ grains), we may cautiously increase them to the maximum quantity—0·5 gramme (7½ grains).

Caffeine, on account of its action upon the heart, is much employed at the present time instead of digitalis. Riegel,[3] having watched its effect upon patients, came to the following conclusion:—Caffeine INCREASES THE CONTRACTILE

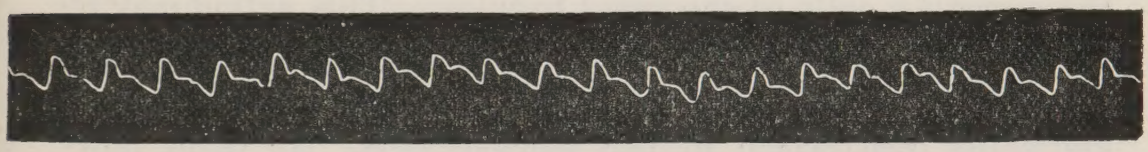
[1] Dietl und v. Vintschgau, 'Arch. f. d. ges. Physiol.,' 1878, Bd. xvi, s. 359.

[2] May it not be due to the action of the drug upon the vaso-motor system? (Translator).

[3] Riegel, 'Verhandl. d. 3. Congresses f. innere Med.,' Wiesbaden, 1884, s. 292; Sahli und S. Frenkel, 'Arch. f. klin. Med.,' 1890, Bd. xlvi, s. 542. For the previous literature see Riegel, and also (since 1864) Koschlakoff, 'Arch. f. path. Anat.,' Bd. xxxi, s. 436.

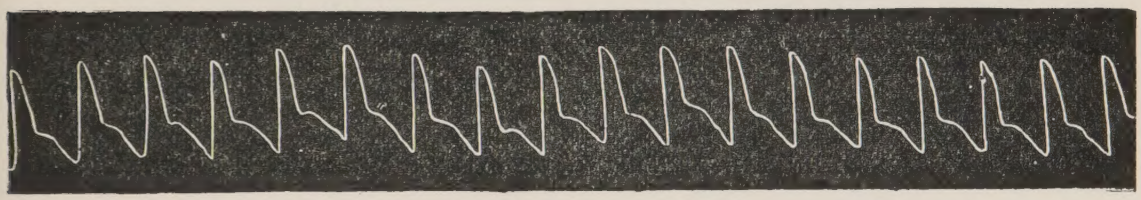
FORCE of the heart, lessens its frequency, and RAISES THE BLOOD-PRESSURE. It rapidly increases the secretion of urine. Its effects are very similar to those of digitalis, but it differs from the latter drug in that it acts more quickly, and has no cumulative tendency. Here are sphygmographic tracings taken in a case of cardiac disease :

FIG. 14.



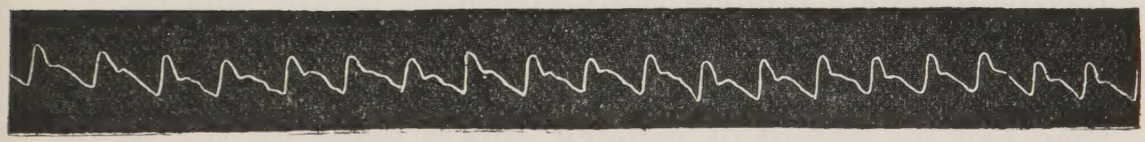
January 26th, without caffeine.

FIG. 15.



February 2nd, during the use of caffeine.

FIG. 16.



February 6th, after caffeine had been discontinued for three days.

Moreover our experience also teaches us that caffeine cannot always replace digitalis in the treatment of diseases of the heart and their sequelæ. Again, it has been noticed[1] that nausea, headache, and vomiting are set up in twenty-four hours by doses, such as 2 grammes (30 grains), of the double salts to which I shall directly refer ; and finally, that the effect of caffeine passes off comparatively quickly.

Further, the above-mentioned experiments upon animals[2] proved that it acts as a general stimulant. An injection of 0·05 gramme of caffeine sufficed in five minutes to put young

[1] Curschmann, 'Deutsche med. Wochenschr.,' 1885, s. 60.

[2] C. Binz, loc. cit., s. 35.

dogs, which were completely narcotised by alcohol, on their legs, so that, though reeling, they ran about and showed signs of being awake. The temperature also quickly rose almost to the normal point.

It has been proved in animals[1] that the diuretic properties of caffeine do not depend upon an increase of blood-pressure or upon a dilatation of the blood-vessels of the kidneys, but that they are due to the direct stimulation by the caffeine of the secreting cells of the renal tubules. This action may be obscured or diminished, if the remedy is given in such large doses as to stimulate the vaso-motor nerves of the kidney, and cause contraction of the blood-vessels. In man, however, with the usual dose necessary to cause diuresis, this is not as a rule to be expected.

The solubility of caffeine is not sufficiently great to make it suitable for subcutaneous injection. This is the principal reason why the following remedies have been introduced.

Caffeinum Natrio-benzoicum, sodio-benzoate of caffeine. A white amorphous powder, or a white granular, odourless mass, with a bitter taste, which forms a clear neutral solution when dissolved in two parts of water or forty parts of alcohol. It contains 44 per cent. of caffeine. The presence of sodium benzoate merely renders the preparation readily soluble.

The dose of sodio-benzoate of caffeine is at least double that of caffeine; though the drug contains somewhat less than half its weight of caffeine, this is made up for by its greater solubility. For example, in threatened acute œdema of the lungs or weakness of the heart, 0·5 to 2 grammes (7½ to 30 grains) dissolved in water would have to be injected under the skin, and this would have to be repeated according to circumstances. The largest single dose of this substance is 1 gramme (15 grains).

Similar compounds of cinnamic acid and salicylic acid have been recommended; they have the same action as the preceding salt.

Theobromine is a more powerful diuretic than caffeine.[2]

[1] W. v. Schroeder, 'Arch. f. experim. Path. u. Pharmakol.,' 1886, Bd. xxii, s. 40; und 1887, Bd. xxiv, s. 85.

[2] W. v. Schroeder, 'Arch. f. exper. Path. u. Pharmak.,' 1887, Bd. xxiv, s. 101.

It is found in the seeds of *Theobroma cacao*, the Mexican cocoa tree; is known chemically as dimethyl-xanthine, *i. e.* caffeine in which one atom of hydrogen has replaced a molecule of methyl, $C_7H_8N_4O_2$. Theobromine is a weak base, in the form of colourless rhombic needles which are soluble in 700 parts of water; it has a bitter taste, and forms salts which are as unstable as those of caffeine. The increase in the secretion of urine caused by it lasts for a longer time than is the case with caffeine; and consequently its action upon the nervous centres is much weaker than that of the latter. The dose for adults should be double that of caffeine.

Experiments on some individuals gave the following results :[1]—Pure theobromine was absorbed with difficulty, but caused diuresis without affecting the heart. THEOBROMINE SODIO-SALICYLATE ("diuretin") was readily absorbed, and is a strong diuretic. Its mean daily dose is 5 grammes (75 grains), which may be given in single doses of 1 gramme (15 grains). Even feeble patients bear it well. It is only after a few days' use that the drug produces its full effect. The sodio-salicylate of theobromine is soluble in half its weight of hot water, and remains in solution when cooled. It should contain 48 per cent. of theobromine.

COFFEE in the form of a hot infusion of the roasted beans is also of some importance from a medical point of view, the more so as it is very largely consumed in Germany, as much as 2·41 kilogrammes (5·3 lbs.) per head being used in 1892.[2] The quantity of tea consumed was only 0·04 kg. ($1\frac{2}{5}$ oz.) per head.

Let us, in the first place, consider what substances are formed in the roasting, and afterwards dissolved in the infusion.

[1] Ch. Gram, 'Therap. Monatshefte,' 1890, s. 10; Aug. Hoffmann, 'Arch. f. exper. Path. u. Pharmak.,' 1890, Bd. xxviii, s. 1; Koritschoner, 'Wiener klin. Wochenschr.,' 1890, No. 39.

[2] 'Statist. Jahrbuch des Deutschen Reiches,' 1893.

Caffeine can stand the heat used in moderate roasting, consequently only a small quantity is dissipated during the process. Almost all of it is dissolved in the infusion, and a cup of good coffee should, on an average, contain 0·12 gramme (1·8 grains).[1] This quantity is enough to produce the effects which I have already described, but of course we must not forget that the stimulating effect of caffeine—at any rate in animals—very soon diminishes; the nervous system becomes tolerant of its action.

According to Aubert, a cup of coffee contains about 0·37 gramme (5·6 grains) of potassium salts, calculated as potassium chloride; a quantity which is not sufficient to produce any effect when absorbed by the intestines. In Curschmann's case of poisoning, to which I have referred, the diarrhœa may have been caused chiefly by these potassium salts.

The products, developed by the roasting, which are contained in the infusion have a certain importance.[2] The first of these is CAFFEOL, a thick dark oil with a strong and very pleasant odour; good coffee contains about 0·05 per cent. of it. Its formula is $C_8H_{10}O_2$, and it is a derivate of benzene. The infusion also contains hydroquinone, $C_6H_4(OH)_2$, formed from the quinic acid of the beans; methylamine, $CH_3.NH_2$, and pyrrol, C_4H_5N, derived from the legumine; also palmitic acid, contained as a glyceride in the raw beans, acetic acid, carbonic acid, apparently a small quantity of acetone, and caffeo-tannic acid, which exist in combination with the caffeine and potassium in the beans.

I made a hot infusion of about 16 to 20 grammes of the best roasted East India coffee, and distilled off the volatile aromatic ingredients. The distillate probably consisted chiefly of caffeol. It was a yellowish liquid with a penetrating coffee-like odour, and became cloudy on cooling. When introduced into the stomachs of young dogs which had been narcotised by alcohol, it increased the number

[1] Aubert, 'Arch. f. d. ges. Physiol.,' 1872, Bd. v, s. 589, and Bd. ix, s. 115.

[2] O. Bernheimer, "Zur Kenntniss der Röstproducte des Kaffees," 'Sitzungsbericht d. Akad. d. Wissench.,' Wien, 1880, Bd. lxxxi, ii, s. 1032.

of heart-beats, doubled the force of the left ventricle's impulse, and doubled the respiratory movements both as regards their number and strength. At the same time, however, the blood-pressure was temporarily diminished. I can only attribute this to a considerable dilatation of the arteries, as the action of the heart was greatly strengthened. This agrees further with what has been observed, namely, that strong coffee causes, in the human subject, marked dilatation of the blood-vessels.

These facts all tend in some degree to suggest, and in some measure to confirm, the view that coffee acts medicinally as a stimulant. The good effects resulting from the use of coffee in threatened cerebral anæmia, fainting, &c., are comprehensible, if in addition to the stimulating action upon the nervous centres, there is a larger supply of blood to these in consequence of the dilatation of the cerebral arteries. This also explains why the energy of the motor centres, when fatigued, is renewed by drinking a cup of coffee. It is a great advantage that this stimulating effect is not followed—as is the case with other stimulants, such as alcohol—by any feeling of exhaustion.

It has also been asserted that coffee DIMINISHES THE TISSUE METABOLISM in the system, and especially that the quantity of urea eliminated is considerably decreased by its use. This is, however, contradicted by the fact that caffeine raises the temperature. Further, a careful consideration of the experiments which have been placed before you, shows that the diminished metabolism is at least not proved, and that the investigations which point to an INCREASED elimination of urea or carbonic acid from the use of coffee[1] are of greater authority. And, finally, recent researches in my laboratory have shown that coffee and caffeine, even if they do alter the consumption of oxygen by warm-blooded animals, do so only to a very slight extent.[2] It is true that coffee diminishes the feeling of hunger and of fatigue, but this has nothing to do with diminished metabolism.

[1] Among these may be included Fubini und Ottolenghi, 'Untersuchungen zur Naturlehre d. M. u. d. T.,' 1883, Bd. xiii, s. 247.

[2] W. Heerlein, "Das Coffein und das Caffeedestillat in ihrer Beziehung zum Stoffwechsel," 'Arch. f. d. ges. Physiol.,' 1892, Bd. lii, s. 165.

A few other effects resulting from the use of strong infusions of coffee must be mentioned. With some people it invariably causes dyspepsia, the mucous membrane of the stomach being evidently unable to tolerate the irritating effects of the pyrogenous products. In others it increases the peristaltic action of the intestines, and with most people an increased secretion of urine takes place after drinking coffee.

The same, in the main, holds good for a hot infusion of Chinese TEA. The amount of caffeine contained in coffee averages 0·6—0·9 per cent., and in tea 1·5—2·5 per cent., a fact which, considering the weight of each substance which is used in preparing the infusion, makes the amount of caffeine taken at one time very much the same in both cases, viz. 0·1 to 0·12 gramme (1·5 to 1·8 grains). The tea leaves are roasted in pans soon after they are gathered, and this develops the aroma, the cause of which has not yet been investigated. GREEN tea consists of leaves which have been roasted when quite fresh; BLACK tea, of leaves which are roasted several times after being dried by exposure to the air for some hours. Many consumers consider the former more stimulating than the latter, but how far they are right is doubtful. The colour of the green tea is often heightened by the addition of a little Prussian blue or indigo.[1]

Tea acts upon the nervous system in the same manner as coffee, and its action upon the intestines is of considerable medical importance. Not a few people are able to take tea with comfort after they have become chronic dyspeptics from the daily use of coffee. This dyspepsia is due to the pyrogenous substances in the coffee, which, as I have already mentioned, are too irritating for the sensitive mucous membrane of the stomach. The quantity of these in tea is quite inconsiderable, but it contains more tannic acid than coffee, as much as 4 per cent. and more being present. The substances contained in the infusion, whatever they are, seem to have a beneficial effect on the alimentary canal.

In prescribing tea as an article of diet it must be borne in mind that it is very frequently largely adulterated.

[1] Flückiger, 'Pharmakognosie des Pflanzenreiches,' 1883, s. 607; see also Bentley and Trimen, 'Medicinal Plants,' 1889, art. 'Camellia Thea.'

This is done to such an extent that in countries such as England, where the consumption is very great, tea which has been used already, is bought, then dried and mixed with parts of plants which have a similar aroma, and with a little tannin, and is sold again in this form. This adulteration can only be detected by microscopical and chemical examination. For cases in which tea has been prescribed therapeutically it is very desirable that the sample should be obtained only from a trustworthy and reliable source.

As regards its history and culture, we find caffeine in five totally different plants, all of which, however, are used. They are the coffee tree (*Coffea arabica*), from Western Asia and the tropical parts of Africa; the tea shrub (*Thea chinensis*), cultivated in China for centuries; the yerba shrub (*Ilex paraguayensis*), the favourite drink and daily requisite of the inhabitants of a large part of South America; the paullinia shrub (*Paullinia sorbilis*), the black seeds of which are chiefly used in preparing a refreshing beverage by travellers in Brazil, and were formerly officinally known by the name PASTA GUARANA; further, the cola tree (*Cola acuminata*), which grows in the tropical parts of Africa, and yields the so-called guru-nuts. This is a greatly valued fruit; it probably contains, besides caffeine, other active ingredients,[1] and is sometimes used as money in the slave trade. The inhabitants of countries so far apart could learn nothing from each other as to the taste of these caffeine-yielding plants, and yet they were discovered and used as an indispensable article of diet in these countries, and thence distributed, as coffee, tea, or yerba, over the whole of the civilised world. This appears to be more than a mere coincidence; it is, in fact, an experimental proof that the parts of these plants containing caffeine produce an agreeably stimulating effect on exhausted nerve-centres. All five plants are roasted in order to develop the particular aroma from the other constituents. Caffeine, as we have seen, is not destroyed by the heat employed in roasting, and, together with the aroma, gives the infusions their stimulating effect.

The cocoa tree (*Theobroma cacao*) of Central America must

[1] Heckel, ref. 'Wien. med. Wochenschr.,' 1890, s. 1243.

be mentioned as the sixth member of this group. Its seeds contain about 1·5 per cent. of theobromine, an alkaloid, the medicinal importance of which has already been discussed. When the Spaniards invaded Mexico they found this tree in a high state of cultivation, the roasted seeds being used by the natives to prepare their national beverage. The best kind were reserved as a privilege for the soldiers of Montezuma. Up to the present day cocoa is the indispensable drink of Spanish soldiers, serving as a food as well as a stimulant. It has the advantage over coffee and tea of being more nutritious, owing to the oil it contains; in addition to this oil chocolate contains an equal quantity of sugar: the absence of the cordial aroma is compensated for by the addition of other aromatic substances. The ancient Mexicans had already made use of vanilla for this purpose.

It is evident that the immoderate use of coffee, tea, and perhaps also of cocoa, must cause debility and insomnia by over-stimulation of the nervous system. Cocoa is least injurious, no doubt owing to the lesser solubility of its theobromine.

Folia Digitalis Purpureæ is a most valuable remedy, the action of which, though somewhat limited in its range of therapeutic usefulness, has been very carefully investigated.

The plant belongs to the Natural Order Scrophulariaceæ, and is a native of Europe, where it grows wild in mountainous districts. It was called digitalis about 1542 by L. Fuchs, a physician and botanist in Tubingen, in allusion to its German name "Fingerhut" or thimble, which its beautiful bell-shaped blossoms resemble. The plant was unknown to the ancient physicians in classical times. It was frequently found to act as a poison, and owing to this its medicinal effects were studied by physicians and gradually applied to therapeutic uses. The very marked FALL IN THE FREQUENCY OF THE PULSE which was noticed in cases of poisoning gave the first clue to its properties. Its use,

however, only became general towards the end of last century, after the publication of W. Withering's elaborate treatise.[1] The first experiments on animals with digitalis were made by C. C. Schiemann in 1786, and described in his Göttingen thesis.

An amorphous yellow bitter powder has been isolated from the plant, and is commercially known as DIGITALINE, but it is not a pure substance, and it varies considerably in its chemical characters. The following bodies[2] have been obtained from the plant, and their properties investigated :— Digitaline, a glucoside which does not crystallise easily; digitaleïne, an amorphous glucoside; and digitoxine, a crystalline body, which is more stable than the glucosides. Of these only digitaleïne is readily soluble in water, digitoxine being quite insoluble. All three possess the specific action of digitalis upon the heart, but the most powerful is digitoxine, which even in a dose of 0·002 gramme ($\frac{1}{30}$ grain) produced, in a young man, marked symptoms of poisoning, which lasted for several days.[3] Digitalis also contains digitonine, a substance which is allied to saponine, a glucoside found in *Saponaria officinalis*. It further contains certain products of decomposition derived from the above-mentioned bodies, some of which are active, some inactive. Digitalis contains no alkaloid. The separate chemical constituents of commercial digitaline have not superseded it; we still only use the fresh infusion of the leaves, the leaves themselves, and the commercial digitaline.

I will now first show you the specific action of commercial digitaline upon the HEART. I inject subcutaneously 0·0005 gramme, which forms a cloudy solution with 0·5 c.c. water, into the back of a strong frog, the heart being exposed.

[1] W. Withering, "An Account of the Foxglove," &c., Birmingham, 1785. [Foxglove was the chief ingredient in an old family receipt for dropsy, which had long been kept secret, and Withering cured one of his friends affected with dropsy of the chest by means of another empirical prescription containing the root. He was then induced to try the effects of the plant in other cases.—Transl.]

[2] Schmiedeberg, 'Arch. f. exper. Path. u. Pharmak.,' 1874, Bd. iii, s. 16, und 1882, Bd. xvi, s. 149; Arnaud, 'Compt. Rend. de l'Acad. des Sc.,' 1889, vol. cix, pp. 679 et 701.

[3] R. Koppe, 'Arch. f. exper. P. und Pharmak.,' 1875, Bd. iii, s. 274.

After a few minutes we notice an increase in the force of the heart's contractions, the diastole of the ventricle becoming somewhat lengthened and the systole more powerful.[1] But the action of the heart soon becomes irregular, and its contraction resembles peristalsis—that is to say, the contraction and relaxation of the individual parts of the heart do not, as before, occur at the same time. Further, the ventricle loses its power to dilate, the expansion becomes less and less, and, in about twenty minutes after the injection, the ventricle comes to a standstill in systole. Mechanical stimulation of it now does not cause the slightest movement. The auricles continue to beat somewhat longer, although at about half their normal rate, but soon they also stop.

The respiratory movements of the frog show no particular change, and if I now set the frog free you will see that it springs up at once like a healthy animal. It is only the heart, therefore, which is strongly affected by the poison.

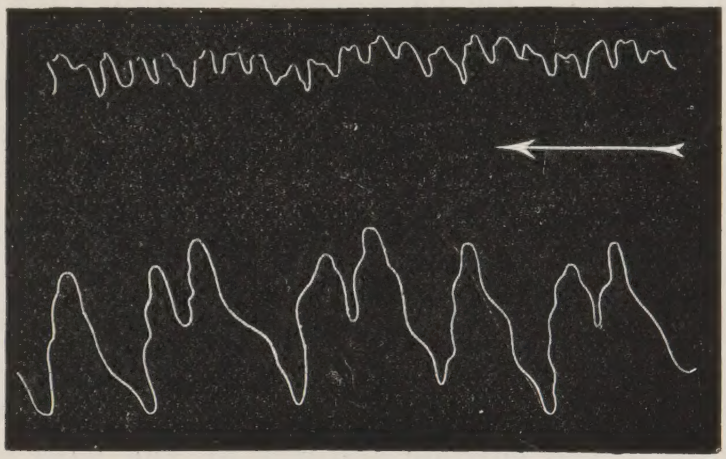
A few centigrammes of morphine were injected into a vein of this dog, which weighs a little over 2 kilos., in order to render it insensible. When the carotids are connected with the manometer, the blood-pressure stands at a little over 100 mm. of mercury. I now inject into the jugular vein several cubic centimetres—one after the other—of a fresh infusion of 2 grammes of digitalis in 50 grammes of water. The mercury rises soon after the first injections, and this increase of pressure becomes so considerable in a little time that by means of the float, to which a white paper ball is attached, it is easily visible to the whole audience. At last the pressure reaches a height of nearly 240 mm. The experiment is now stopped, for its continuation would cause the pressure to fall to zero, and would result in complete death of the heart, just as we saw before in the case of the frog. Let us now analyse the details.

1. The BLOOD-PRESSURE RISES in the aorta. The primary cause of this is the direct action of digitaline upon the heart itself, for digitaline causes this rise of blood-pressure even when the action of the vagi is suspended through the application of atropine, and also when the cardiac branches

[1] F. Williams, ibid., 1881, Bd. xiii, s. 1.

have been divided. The force of single contractions of the ventricle is sometimes four to six times greater than the normal; the pulse is stronger and markedly dicrotic, the dicrotism always being upon the descending portion of the pulse-curve. This proves, therefore, that the diastole is prolonged in the mammal as well as in the frog. The

FIG. 17.



tracings[1] represented in the accompanying figure were taken before and a little after the injection of an infusion of digitalis into the carotid of a dog, both vagi having been previously divided in the neck.

Traube refers the increased action of the heart to stimulation of its excito-motor nerves. This may be so, but as the result is essentially the same in a heart removed from a frog as it is in the case of a warm-blooded animal which has not been interfered with, and as the muscular tissue of the heart is affected, there must be a direct relation between the cardiac muscle and the poison. A kind of tetanus follows this stimulation. The heart becomes bright red, bloodless, hard, and sometimes angular. It appears like altered parenchymatous tissue, and does not respond to any external stimulus.

The increased blood-pressure has also been referred to a contraction of the arteries caused by digitaline.[2] We know

[1] Böhm, 'Arch. f. d. ges. Physiol.,' 1872, Bd. v, s. 186.

[2] Ackermann, 'Arch. f. klin. Med.,' 1872, Bd. xi, s. 125; L. Brunton and A. B. Meyer, 'Journ. Anat. and Physiol.,' 1873, vol. vii, p. 134.

that if the quantity of fluid in the arterial system remains the same, the blood-pressure depends upon three factors—that is to say, it is increased (i) when the ventricle contracts strongly; (ii) when the ventricle contracts frequently; and (iii) in proportion to the resistance caused by the more or less marked "tone" (*i. e.* by the contraction) of the whole arterial system. By means of digitalis this "tone" may be increased in an animal by stimulating the vaso-motor centre or the arterial wall. The case probably stands thus :—Weak doses of digitaline readily raise the arterial tension by means of a central and peripheral stimulation of the vaso-motor nerves; strong doses increase this at first, but diminish it afterwards.

2. The RATE OF THE PULSE FALLS as a rule. This is at first due to a central and peripheral stimulation of the vagi, for if these nerves have previously been divided, the diminution in the rate of the pulse which is brought about by the injection of digitaline is smaller, whilst the rate is not altered at all if the cardiac endings of the vagi have been paralysed by atropine. This view, which has been advocated more particularly by Traube, is opposed by A. B. Meyer, who has advanced another and very noteworthy theory,[1] which agrees with the view of C. Ludwig, and is as follows :—The blood flows through wide openings at different rates in and out of the brain, which is surrounded by an unyielding skull. The tension of the brain undergoes corresponding changes. Every one of these changes is felt at once as an increased or decreased stimulus, and in this way every change of pressure in the cavity of the skull must act upon the organs of the body. The vagus centre which is enclosed in this cavity will react to any INCREASED pressure by DIMINISHING the rate of the heart, and will thus prevent too great a supply of blood passing to the brain, just as a diminution in the rate of the pulse is one of the earliest symptoms of increased brain-pressure arising from any other cause.[2]

Traube answers this by pointing out that digitalis, even

[1] A. Fick, 'Untersuchungen a. d. physiol. Labor zu Zürich,' 1869, s. 71.

[2] Leyden, 'Arch. f. pathol. Anat.,' 1867, Bd. xxxvii, s. 538.

after section of the cervical cord, whereby the blood-pressure throughout the system is very much reduced, decreases the rate of the pulse, therefore this must be due to a direct stimulation of the vagus. But both of these explanations are tenable, and what one emphasises does not contradict the other.

I show here the pulse tracings of a dog of 14 kilos. weight, copied from one of the recent[1] numerous works upon this subject. *A* shows the normal condition ; *B* the state after an injection of 0·014 gramme of digitaline into a vein ; and *C* the later toxic acceleration produced by the drug.

FIG. 18.

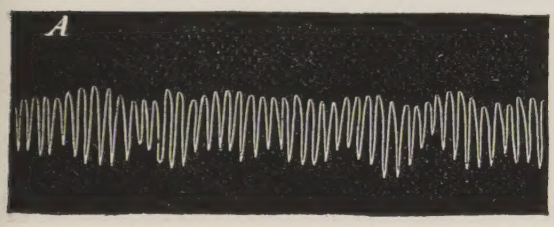


FIG. 19.

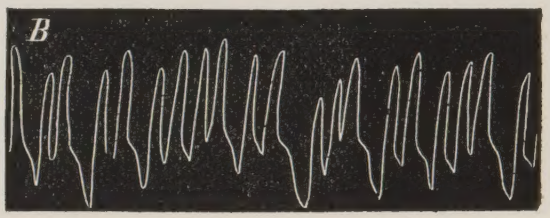
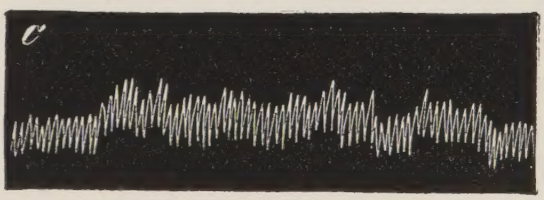


FIG. 20.



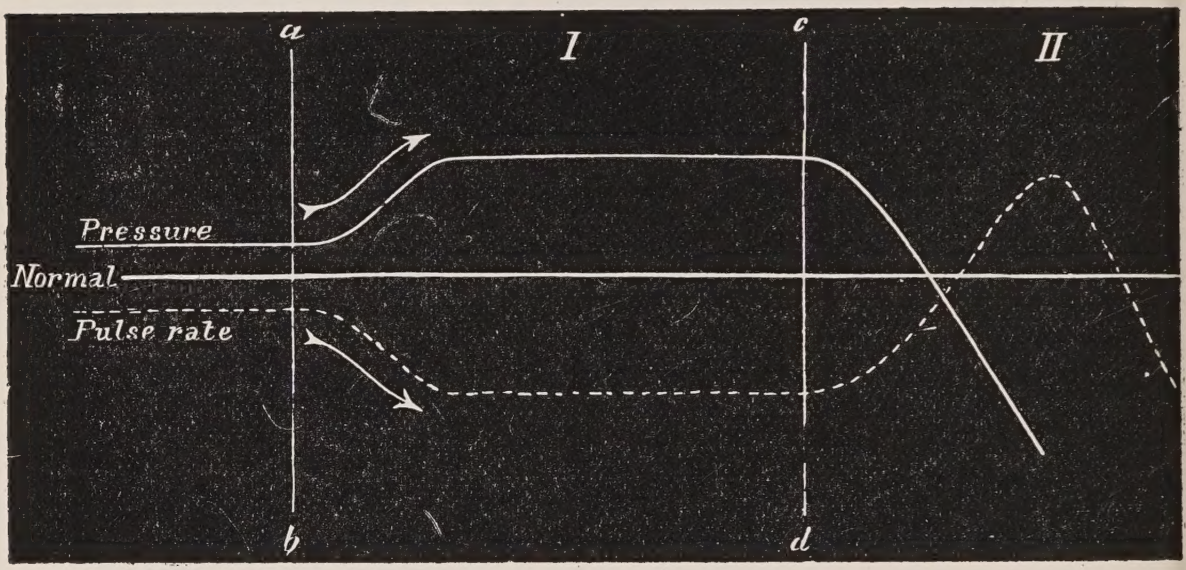
The conditions are altered by the further effects of larger doses. The blood-pressure falls below the normal, and continues to sink, while the radial pulse is hardly perceptible; the latter, which at the commencement of the experiment was slow and regular, soon becomes very rapid, irregular, and intermittent. In the one case the irritation of the cardiac muscle, in the other the irritation of the vagus, is succeeded by paralysis.

We may represent these changes in the blood-pressure and pulse produced by the action of digitaline by a simple diagram. Let us take the middle line as the normal condition of both. The upper line, representing the arterial pressure, and the dotted line, the pulse-rate, run at first parallel to it, and represent, therefore, the condition of the

[1] M. Kaufmann, ' Revue de médecine,' 1884, vol. iv, p. 381.

healthy heart before it is acted upon by digitaline. *a b* marks the commencement of the effect produced by a moderate dose of digitaline, *c d* the effect of a poisonous

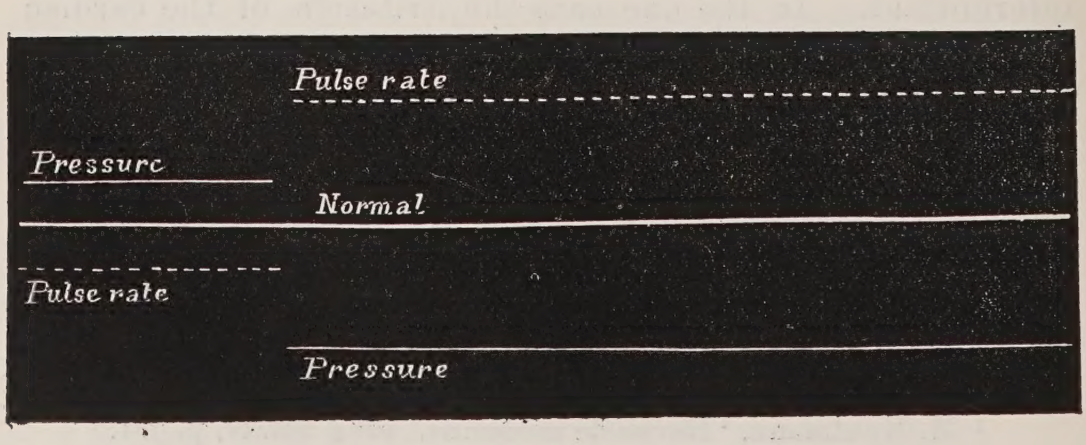
FIG. 21.



dose; in I the pressure rises above the normal and the pulse-rate falls; in II both change in an opposite direction, and death takes place through paralysis of the heart.

My diagram—in which naturally the times of the ascent and descent of both lines do not correspond with every single case—gives us an insight into the therapeutic effect of digitaline in many cases of heart disease. There are cases of heart disease in which the blood-pressure is lowered and the pulse-rate is increased. The following diagram represents such a case.

FIG. 22.



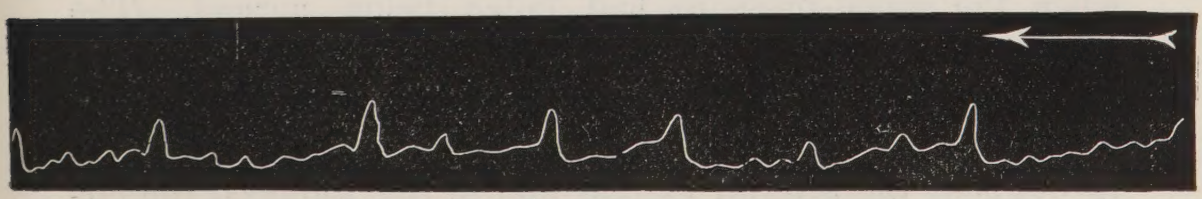
In comparing this diagram with that representing the first stage of the action of digitaline, it is obvious that the one condition neutralises the other; and this result is also produced in patients suffering with heart disease.

Such patients present the following symptoms: irregular and very rapid pulse, impeded pulmonary circulation with consequent shortness of breath, and pulmonary catarrh; the arteries are imperfectly filled with blood, and the veins are distended. Consequently cyanosis, a feeling of chilliness, imperfect nutrition, dropsy in the areolar tissue of the lower extremities and in the peritoneum, and great diminution in the urinary secretion are met with. The use of digitalis generally relieves these symptoms in a few days, if the remedy is carefully administered.

Withering has already described how the pulse becomes reduced in frequency. For this reason, until the works of Traube[1] appeared, digitalis was supposed, from a clinical point of view, to act as a sedative. This idea was supported by the fact that in cases of poisoning by the drug death resulted from paralysis of the heart. We know now that digitalis chiefly acts, not by lowering the action of the heart, but by regulating and strengthening it, and that, consequently, the diminished frequency of the pulse is only a symptom of minor importance.

Here are two sphygmographic tracings which I took some time ago in our Clinic, from the pulse of a woman suffering

FIG. 23.

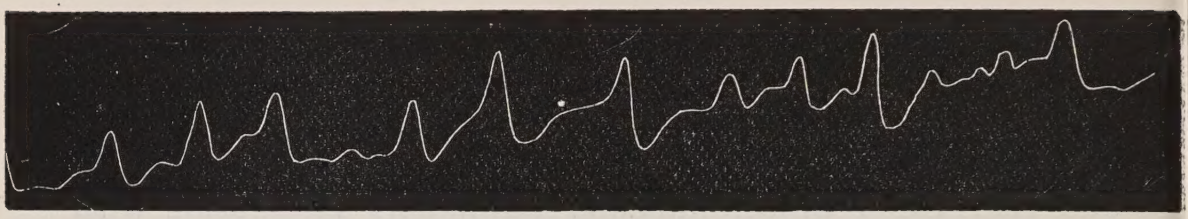


from myocarditis. The first one shows the condition before the application of any remedy.

The second one was taken after I had given 2 grammes (30 grains) of powdered digitalis in the course of a few days.

[1] M. Traube, 'Charité-Ann.,' Berlin, 1850, Bd. i, s. 622, und 1851, Bd. ii, s. 18; and in numerous other periodicals.

FIG. 24.



The difference is very striking; the pulse has been reduced by about one third in frequency, and its quality is distinctly better. The elevations, which for the most part were hardly visible, have everywhere become very marked. The systole is strong and continuous, the diastole shows a nearly normal dicrotism, and the rhythm is almost regular. If we had measured the blood-pressure in this patient, the resulting change for the better would also have been clearly shown.

The effect which digitalis has of equalising the circulation and of removing a state of passive congestion of the kidneys is an important indication for its use as a DIURETIC. It only acts as such, in those cases in which the decrease of the urine, and the dropsy, depend on some heart mischief. Digitalis has no direct action upon the kidney tissue like other remedies. On the contrary, it has been shown that the secretion of the urine is largely DECREASED or completely suppressed when digitaline is given to healthy animals, while at the same time the blood-pressure is very much increased. In some experiments the secretion was restored as soon as the blood-pressure fell, in others only when the blood-pressure had fallen below normal. The explanation of this is that the vaso-motor nerves of the kidneys are more strongly stimulated by digitaline than other nerves, so that, notwithstanding the increased pressure throughout the arterial system and in the kidneys, the circulation and the secretion in these organs are impeded. The urine then always contains albumen, which we know is also the case when, from any temporary mechanical cause, the circulation in the kidneys is interfered with.[1] Heidenhain has proved that the quantity of the urine need not be

[1] L. Brunton and Power, 'Proceedings of the Royal Soc.,' 1874, No. 153.

augmented by an increase of blood-pressure, and that some other factor must take part in its production.[1]

Digitaline is a very good diuretic, but only in those cases in which the conditions indicating its use are present—that is to say, in most cases of heart disease. Heart disease causes venous congestion in the tissues, but venous congestion lessens the quantity of water in the urine and increases that in the lymph. Digitaline removes this cause of the dropsy. Dropsy resulting from cirrhosis of the liver, or the cachexia of cancer, &c., is not relieved by it. It is of no use to prescribe digitalis in such cases, though this is often done by physicians who do not trouble themselves about pharmacology. Digitalis only does harm under such conditions.

The detailed discussion of those forms of heart disease, in which digitalis is of value, belongs more particularly to clinical medicine.[2] I will only mention that a case of FATTY DEGENERATION OF THE HEART, in which dropsy and albuminuria had already supervened, was regarded as cured, or at any rate improved, by a prolonged use of digitalis and iron.[3] There is nothing impossible about this view. Digitaline has a specific effect on the cardiac muscle, increasing its action by moderate stimulation, and therefore we are justified in believing that small and frequently repeated doses help its nutrition and remedy its derangements just as exercise, electricity, and massage do in the case of other muscles.

The following observations with regard to the TEMPERATURE after the administration of digitaline, have been made on healthy dogs (Ackermann). The decrease of the pulse-rate and the increase of the blood-pressure were followed by a fall of temperature (taken in the RECTUM), which became more marked as the pressure increased. As soon as this began to fall the temperature began to rise, and if the pressure fell considerably below the normal with the onset of paralysis of the ventricle, the temperature in the rectum rose above the normal. THE TEMPERATURE OF THE SURFACE

[1] 'Handb. d. Physiol.,' Bd. v, i, s. 324.

[2] See F. Penzoldt, 'Münch. med. Wochenschr.,' 1886, No. 42.

[3] H. Seiler, 'Arch. f. klin. Med.,' 1875, Bd. xv, s. 123; G. Mayer, 'Ueber heilbare Formen chronischer Herzleiden,' Aachen, 1881, s. 22.

OF THE BODY, measured between the toes, varied in precisely the contrary way; during the rise of blood-pressure there is an increase in the temperature of 0·5° C. (0·9° F.). This can only be explained as follows.

The increased blood-pressure fills the peripheral arteries better and more continuously with blood which has been warmed in the internal parts of the body. In the skin the blood parts with its heat more continuously and readily to the surrounding atmosphere, the temperature of which is 20° C. (36° F.) lower. If, on the other hand, the heart works feebly and insufficiently the peripheral vessels remain relatively empty, and almost all the blood accumulates in the large internal veins; the loss of heat from the skin to the cool air is diminished, but the temperature of the rectum is increased, for the thermogenetic changes in the body have not been interrupted.

The CUMULATIVE action of preparations of digitalis has long been recognised as unpleasant and dangerous. This action is shown by poisonous symptoms sometimes arising when the drug is given continuously in moderate doses, and even after it has been discontinued. This cumulative action is probably due to the fact that the chief constituents of digitalis are absorbed with comparative difficulty, and may also be slowly eliminated, and consequently accumulate in the system.

Besides this cumulative action of digitalis there are other unpleasant drawbacks to its use. It is liable to produce catarrh of the stomach, DISORDERED DIGESTION, and DIARRHŒA. In some cases these conditions contra-indicate the use of the drug, in others they must be looked upon as minor evils, and in others again they can be modified by the use of small doses of opium. That digitalis possesses these irritating properties has also been proved experimentally, for digitoxine causes great pain and inflammation[1] when subcutaneously injected, even in very minute quantities (fractions of a milligramme).

A patient who is taking digitalis must be careful not to sit up suddenly in bed, and must avoid even slight bodily

[1] Koppe und P. Kaufmann, 'Arch. f. exper. Path. u. Pharmak.,' 1889, Bd. xxv, s. 397.

exertion, otherwise sudden and final stoppage of the heart may be the result.

Another special use of digitalis must be mentioned, namely, its employment as an ANTIPYRETIC. It was recommended for this purpose especially by Traube, owing to the effects, to which I have already referred, and was in considerable vogue for some time. The report "Ueber den Nutzen der Digitalisanwendung im enterischen Typhus,"[1] from the Leipzig Clinic, is very instructive. It is there stated that by means of digitalis the fever is diminished, the delirium lessened, and that the pulse, though very small, grows fuller and remains so; that Bright's disease does not contra-indicate the use of the drug, and that dangerous collapse need not be feared if proper care is exercised; but we learn at the same time that digitalis increases catarrh of the stomach and seems to prolong the disease. Out of eighty cases, thirty-five ended fatally—that is to say, 43·7 per cent.—a sufficiently significant fact. Most physicians have discarded the use of digitalis in febrile conditions, and it is only used as an antipyretic by those who still cling to the doubly false idea that digitalis in therapeutic doses LESSENS the work of the heart, and that the supposed slowing of the circulation thereby produced is accompanied by diminished oxidation.[2]

Digitalis, in addition to other antipyretic drugs, is only to be recommended[3] in occasional obstinate cases of acute fever with a continuous high temperature, in which the pulse is very small, the blood accumulating in the large internal veins, the pale burning skin never appearing to become cooler—in cases, that is to say, which present some conditions similar to those which exist in valvular disease. Digitalis, by increasing the blood-pressure and rendering the circulation through the skin more rapid, causes a decrease of temperature. In similar cases, however, in which the blood-pressure is normal or increased—for the blood-pressure in fever may be either normal, increased, or decreased[4]—the

[1] E. Hankel, 'Arch. d. Heilkunde,' 1869, Bd. x, s. 280.

[2] See D. Finkler, 'Arch. f. d. ges. Physiol.,' 1875, Bd. x, s. 368.

[3] Liebermeister, 'Path. u. Therapie d. Fiebers,' 1875, s. 642; Jürgensen, 'Croupöse Pneumonie,' 1883, s. 314.

Riegel und Reichmann, 'Deutsche med. Wochenschr.,' 1889, No. 38.

action of digitalis as an antipyretic is as feeble as is its action as a diuretic under the same conditions. Even when digitalis does lower a febrile temperature it does not do so, according to Traube, until thirty-six hours after its first administration.

The leaves are still the most reliable and convenient FORM IN WHICH TO ADMINISTER digitalis in practice, especially when given as a POWDER. This is largely due to the fact that their active ingredient is digitoxine, which is insoluble in water, so that hardly any of it is contained in the infusion. Digitoxine, however, is separated in the intestines from the leaves and absorbed. Again, it is possible that when the leaves are treated with hot water, a part of the essential constituent is decomposed into toxiresine, &c.

The largest single dose is 0·2 gramme (3 grains); the largest amount to be given in a day 1 gramme (15 grains).

Pure digitaline and digitaleïne are soluble in water, and have a slightly stronger action, but they are very troublesome to prepare in a pure form. Consequently the only preparation we have, besides the leaves, is the TINCTURE OF DIGITALIS, which is prepared by macerating five parts of the fresh crushed leaves in six parts of alcohol.[1] The largest single dose of this is 1·5 grms. (25 minims); the largest quantity to be given in a day 5 grms. (85 minims). Leyden has also given the tincture subcutaneously to ward off acute œdema of the lung, when the action of the left ventricle seemed to be rapidly failing. He says that he obtains the effect of the drug most quickly when given in this way.

The strength of digitalis leaves, like that of all other vegetable drugs, varies according to the year and the locality in which they were grown, and the length of time they have been kept. It is unintelligible to me why we do not prescribe the commercial digitaline in Germany,[2] for this has been done elsewhere for a long time. It is, to be sure, not of uniform strength, but it is certainly more trustworthy

[1] The tincture of digitalis (Brit. Pharm.) is prepared by macerating ONE part of the DRIED leaves in EIGHT parts of proof spirit. The dose is 10 to 30 minims. (Transl.)

[2] Bouchardat, 'Manuel de Matière médicale,' Paris, 1873, p. 685.

and durable than the leaves and their preparations. The dose to commence with is 1 milligramme ($\frac{1}{66}$ of a grain) twice a day; 0·003 gramme ($\frac{1}{22}$ of a grain) during the day should be sufficient for any case.[1] If we take care to obtain digitaline from a good source, where it is always prepared in the same manner, we may then administer it with confidence.

Numerous cases of POISONING by digitalis are on record, the most frequent cause being the misuse of the medicinal preparation.

It happened[2] that two young girls, mistaking the leaves of digitalis for the hairy leaves of borage (*Borago officinalis*), used them in a salad and became ill. The daughter of a druggist fell into the same error. She drank some tea which she had prepared from 7 grammes (105 grains) of digitalis leaves instead of borage, and died five days afterwards.[3]

Jörg[4] and his assistant, experimenting upon themselves, suffered from marked symptoms of digitalis poisoning. Their results were not, however, commensurate with the risk they incurred.

N. Görz, of Dorpat, experimented with pure digitaleïne, taking pills for ten days. Each pill contained 0·001 gramme ($\frac{1}{66}$ of a grain), and he commenced with one pill, but increased the number to five daily. His PULSE fell from 54 to 46, but became fuller and stronger; its rate also was very EASILY AFFECTED, and would suddenly rise after very

[1] M. Semmola, reprint from the 'Internat. klin. Randschau,' 1888.

[2] Hasselt-Husemann, 'Handb. d. Toxikol.,' 1862, s. 451.

[3] A. Mazel, 'Gaz. des hôpit.,' 1864, p. 301.

[4] Jörg, 'Materialien zu einer zukünftigen Heilmittellehre durch Versuche der Arzneien an gesunden Menschen,' Leipzig, 1825, Bd. i, s. 444.

slight movement TO 128 IN THE MINUTE. In addition to this Görz had slight headache, impaired appetite, and a feeling of great exhaustion and oppression in the cardiac region.[1]

As regards THE GREAT IRREGULARITY OF THE HEART above mentioned, the following case[2] is very instructive :—A man, twenty-two years old, procured some pills containing digitalis for the purpose of malingering, and took 0·9 gramme of the leaves every day. In this way he took 17 grammes (about 4 drachms) within a few weeks. He suffered from violent pain in the region of the stomach, loss of appetite, headache, vomiting, and dizziness ; he looked miserable ; his breath was offensive, his tongue thickly coated, and he complained of loss of vision and great weakness in the limbs. The temperature was not altered, and the pulse was only 52 in the minute. The patient fainted one day when he sat up in bed to have his throat examined, and, on getting out of bed on the same day to pass a motion, he fell down and died in a few moments. Certain other reasons, together with the mode of death, necessitated an inquest which cleared up the case.

Two groups of symptoms in this case are important : the first, associated with the alimentary canal, requires no further explanation ; the second concerns the heart. In this case we see the irritability of the heart, to which reference is made in the experiments by Görz, increased to such an extent as to stop its action. This corresponds with what is generally observed in healthy individuals, namely, that the pulse-rate depends to some degree upon the position of the body, and still more upon any muscular exertion. A man's pulse is more frequent when he is standing than when he is sitting, and least frequent when he is lying down ; every muscular effort increases the action of the heart. From what I have previously said, it is obvious that a heart under the influence of digitalis can be easily overtaxed and paralysed. I will just mention, here, that in cases of convalescence after protracted infectious diseases, sitting up suddenly in bed may lead to this result, even when digitalis

[1] N. Görz, 'Unters. über d. Natiwelle'schen Digitalispräparate,' Dorpat, Doctordissertation, 1873, s. 46.

[2] C. Köhnhorn, 'Vierteljahrschr. f. gerichtl. Med.,' 1876, Bd. xxiv, s. 278.

has not been given ; considerable increase in the pulse-rate is quite a common symptom in these cases, fainting fits frequently occur, and sudden death from cardiac failure has been observed.

The intentional poisoning of a lady by her medical attendant in Paris in 1863[1] caused a great sensation. The physician who was called in, found the patient pale and extremely weak, very excited, covered with cold perspiration, vomiting frequently, and complaining of unbearable pain in the head. Her pulse was irregularly intermittent, and then became imperceptible, a condition which seemed to be due to internal hæmorrhage. Death soon took place. The fact, which could be proved, that 3·5 grammes (52½ grains) of digitaline had been in the possession of the so-called homœopath, and that nearly 2·5 grammes (37½ grains) of this had been used, pointed to the probability that this poison had been the cause of death. The body was exhumed thirteen days after, and extracts were obtained from the contents of the stomach, and from the dried vomited matter scraped off the floor, which, on being administered to animals, caused death in the manner characteristic of digitaline. This evidence completed the proof, and resulted in the conviction of the accused.

The two experts do not seem to have employed any of the CHEMICAL TESTS for digitaline, but there are some which are easily applied—for example, digitaline may be isolated by alcohol or chloroform, and the residue dissolved in water. I have here such a solution of 1 in 1000 of commercial digitaline ; I add to it two drops of nitric acid and a little phospho-molybdic acid, which colours the mixture yellow, and makes it cloudy. On heating, this clears up and becomes a beautiful light green. On cooling the solution, and adding a little ammonia, it turns blue, but on heating it again, it becomes colourless.

There are a number of plants which contain substances possessing the same physiological properties as the constituents of digitalis, but only two of them have as yet gained any permanent place as therapeutic agents.

[1] Tardieu et Roussin, "Affaire Couty de la Pommerais. Etude, &c., sur l'empoisonnement," Paris, 1875, p. 809.

1. Bulbus Scillæ, squill, sometimes called sea-onion, consists of slices cut transversely from the inner part of the bulb of the *Urginea maritima* (*Scilla maritima*), which on an average are 3 mm. thick, are yellowish white, transparent, with transverse cracks, and disagreeably bitter in taste. They contain scillitine, a non-nitrogenous amorphous glucoside, soluble in alcohol, but only with difficulty in water. This has a fatal effect upon dogs, even in doses of 0·001 gramme for each kilo. of their weight.[1] Vomiting and diarrhœa, peripheral muscular paralysis, and early cardiac failure are among the symptoms mentioned. Squill contains, however, only a small quantity of scillitine. The above-mentioned symptoms were observed also in cases of poisoning[2] reported in former years, as well as in recent experiments on animals. The bulb is far more poisonous when fresh than when dried. As regards its action on the heart, scillitine resembles digitaline, and what has been stated with regard to the effects of the latter holds good, in some measure, also for the former.

Squill is seldom used by physicians now-a-days, but is added to popular remedies for promoting diuresis, and sometimes a little too much is taken in this form. The tincture, the vinegar, and the oxymel scillæ, the last a nauseous mixture of the vinegar with honey, are officinal. The dose of the tincture is ten to twelve drops, that of the vinegar thirty to thirty-six, whilst a teaspoonful is given of the oxymel.

2. Semen Strophanthi, strophanthus seeds. The opening up of Africa has brought to our knowledge several new poisons, of which the arrow poison, kombi, of the Zambesi negroes has acquired some importance in medicine. This new remedy offers a good instance of the way in which such discoveries are made. The following is the account given by two missionaries:[3] "The poison used here, and called

[1] v. Jarmersted, 'Arch. f. exper. Path. u. Pharmak.,' 1879, Bd. xi, s. 22.

[2] Wibmer, 'Wirk. d. Gifte u. Arzneimittel,' 1842, Bd. v, s. 19; lately E. B. Trumann, 'Lancet,' 1886, vol. ii, p. 390 (Four children poisoned by a "cough mixture").

[3] 'Narrative of an Expedition to the Zambesi and its Tributaries, 1858–64,' by David and Charles Livingstone, 1865, pp. 446–7; Th. R.

KOMBI, is obtained from a species of *Strophanthus*, and is very virulent. Dr. Kirk found, by an accidental experiment on himself, that it acts by lowering the pulse. In using his tooth-brush, which had been in a pocket containing a little of the poison, he noticed a bitter taste, but attributed it to his having sometimes used the handle in taking quinine. Though the quantity was small it immediately showed its power by lowering his pulse, which at the time had been raised by a cold, and next day he was perfectly restored. Not much can be inferred from a single case of this kind, but it is possible that the kombi may turn out a valuable remedy."

Strophanthus, in sufficiently large doses, acts as a poison, producing a distinct effect upon the heart, similar to that of digitalis. It differs, however, from this in acting more quickly and in not disturbing the intestinal canal, whilst it does not possess the cumulative action of digitalis.[1] These properties are of great value in therapeutics.[2] The good results derived from strophanthus are, on the other hand, certainly not so lasting as those which follow the use of digitalis. Strophanthus appears, in addition to its other actions, to have a quieting effect on the brain and the medulla oblongata. This has been observed to follow its use in that form of dyspnœa which so often accompanies diseases of the heart and kidneys.

The TINCTURE, as well as STROPHANTHINE, is prescribed, the former being officinal in Germany. It is prepared by digesting one part of the seeds, freed from their oily matter, in ten parts of alcohol; its largest single dose is 0·5 grm. (8 drops), the largest quantity to be given in the day 2 grms. (35 drops). It is said to readily cause vomiting.

Fraser, "*Strophanthus hispidus*: its Natural History, Chemistry, and Pharmacology," Edinburgh, 'Trans. Roy. Soc.,' 1890, vol. xxxv, s. 955; 1891, vol. xxxvi, s. 343.

[1] Paschkis u. Zerner, 'Med. Jahrbücher,' Wien, 1887, s. 513; E. Steinach, 'Wiener klin. Wochenschr.,' 1888, Nos. 21 und 22; Langgaard, 'Therap. Monatshefte,' 1887, s. 306.

[2] R. Demme, 'Bericht über das Kinderhospital in Bern für 1887,' s. 67; Langgaard, 'Therap. Monatshefte,' 1887, s. 180; E. Pins, ibid., ss. 208 und 261; H. Hochhaus, 'Deutsche med. Wochenschr.,' 1887, Nos. 42 und 43; G. Sée et Gley, 'Progrès méd.,' 1888, No. 46.

Pure strophanthine has been prescribed with good results in doses of 0·0002—0·001 gramme ($\frac{1}{300}$ to $\frac{1}{60}$ of a grain). We must commence with the lowest dose, and can then gradually and carefully increase it. It is a white crystalline powder, having a neutral reaction and very bitter taste, and is soluble in 40 parts of water. Its probable formula is $C_{16}H_{26}O_8$.

A species of hellebore, VERATRUM VIRIDE, American hellebore, containing HELLEBOREÏNE, which acts exactly like digitalis, and can be obtained fairly free from adulteration, may be included here. In addition to these there are *Nerium oleander* and OLEANDRINE, *Adonis vernalis* and ADONIDINE, *Apocynum cannabinum*, officinal in North America, and APOCYNINE, *Convallaria majalis* and CONVALLAMARINE, and others,[1] which, however, are practically of very little value.

[1] Marmé, 'Zeitschr. f. rat. Med.,' 1866, Bd. xxvi, s. 1; Husemann und König, 'Arch. f. exper. P. u. Pharm.,' 1876, Bd. v, s. 228; Schmiedeberg, ibid., 1882, Bd. xvi, s. 149; G. Leubuscher, 'Zeitschr. f. klin. Med.,' 1884, Bd. vii, s. 587; Ringer and Sainsbury, 'Med.-Chir. Transactions,' 1884, vol. lxvii.

XII.

Secale cornutum—Botanical characters—Active ingredients—Therapeutic use — Preparations — Ergotism in former days and at the present time—Three new remedies which act on the uterus : the rhizome of Hydrastis Canadensis, the root-bark of Gossypium herbaceum, the root-bark of Viburnum prunifolium.

Ergot is used to increase the action of the uterus in the same manner as digitalis is used to increase the action of the heart.

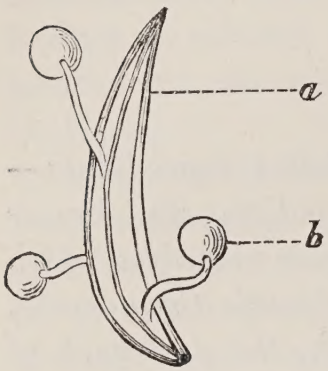
Secale cornutum is the sclerotium of *Claviceps purpurea*, which is collected whilst its growth is inactive. The grains are subcylindrical or obscurely triangular, generally arched or curved, varying in length from about one third of an inch to an inch and a half, and in diameter from half a line to four lines. They are violet, brown, or blackish externally, longitudinally furrowed, and of a firm structure. They have little taste when fresh, but subsequently are mawkish.

The development of the fungus—if we begin with the sclerotium or stroma—takes the following course :—When fresh ergot is placed under a thin layer of moist earth, small mushroom-like bodies begin to sprout in a few months from the sclerotium, the stalks growing to a length of 4 cm. These little spherical tops (*receptacles*) have externally numerous small flask-shaped cavities (*perithecia*) full of elongated sacs (*asci*), each of which contains several thread-like spores (*ascospores*). When these spores happen to fall on grains of rye, wheat, barley, or other Gramineæ, they destroy the tissue, increase, and ultimately form new sclerotia like the one which produced them.

In mycology ergot is also called the sterile, whilst the sprouting mushroom-like body is called the fertile sporangium of the fungus *Claviceps purpurea*.

The accompanying figure is a diagrammatic representation of the mode of development: *a*, ergot or sclerotium; *b*, the mushroom-like sprouts, containing the thread-like spores.

Fig. 25.



The Chinese are said to have made use of ergot in midwifery[1] at a very early date. German physicians of the sixteenth century mention its effects in such cases. Apparently the first to do so was Adam Lonicerus, of Frankfort-on-the-Maine, in his 'Kräuterbuch' of 1582. We have continued to use the drug, but it seems to have been employed in other countries only towards the end of last century. Desgranges[2] relates that he found that ergot was used by midwives in Lyons in 1777, and consequently he was induced to try it in his practice. In England it was owing to the writings of Stearns (1807) and Prescot (1813) that it became known and generally employed.

Ergot is chiefly imported from Russia, and to a smaller extent from Spain.[3]

It has a specific action on the uterus and brings on labour pains, which do not differ at all from normal ones, their frequency, especially, being increased in the human subject. The action of the drug begins to show itself about fifteen minutes after its administration, and exerts its full effect in another quarter of an hour.[4] I preface the discussion of this subject with the above statements of a eminent contemporary accoucheur, because the action of ergot has been denied altogether, owing to certain causes into which we shall inquire later on.

In endeavouring to explain the results produced experimentally by ergot, much stress has sometimes been put on a

[1] See St. Julien, 'Compt. Rend. de l'Acad. des Sc.,' 1849, vol. xxviii, p. 196.

[2] Desgranges, 'Observations pratiques sur l'administr. du Seigle Ergoté contre l'inertie de la matrice,' Montpellier, 1882.

[3] Kobert, 'Historische Studien aus dem Pharmak. Institut zu Dorpat,' 1889, ss. 1 bis 48.

[4] Schatz, 'Centralbl. f. Gynäkol.,' 1889, s. 564.

supposed profound modification of the general as well as the local circulation of the blood. It is true that the single labour pains caused by ergot, or its constituents, seem to be accompanied at first by anæmia of the uterus;[1] but when we observe the action of ergot in a healthy woman in labour, it is obvious that any great change in the condition of the vascular system is altogether out of the question. We see that the remedy can stop hæmorrhage from the uterus by increasing the labour pains, without any other change making itself felt in the organism, a fact which points definitely to a locally stimulating and distinctly limited action of the ordinary doses. This action, however, may of course depend upon the nerves of the organ or on its blood-vessels.[2]

A great increase in the secretion of urine has often been observed to accompany the action of ergot.[3]

The active constituent of the drug has been diligently searched for, but up to the present time without any satisfactory results. Opinions have been more varied, and discussions more heated, with regard to ergot than in the case of any other drug. This is due to the chemical instability of the active constituent. I pass over the views held in former years as regards the action of ergot, which have since been discarded as altogether erroneous,[4] and shall only give you the most recent,[5] which are in accordance with all that has been published regarding the investigations hitherto made in this subject.

There are two bodies in fresh ergot which cause labour pains, the alkaloid CORNUTINE, and SPHACELINIC ACID. In pregnant animals the first organ to be affected by the action of cornutine is the uterus, and the further pregnancy is advanced, the more violent are the pains; if labour pains

[1] Rossbach und Nikitin, 'Pharmakol. Untersuchungen,' Würzburg, 1879, Bd. iii, s. 78.

[2] M. Marckwald, 'Zeitschr. f. Geburtsh. u. Gynäkol.,' 1884, Bd. x, s. 397.

[3] A. Wernich, 'Centralbl. f. d. med. Wissensch.,' 1873, s. 353.

[4] Kobert, loc. cit., 43.

[5] Kobert, "Ueber die Bestandteile und Wirkungen des Mutterkorns," 'Arch. für exper. Path. u. Pharmak.,' 1884, Bd. xviii, s. 316; 'Centralbl. f. Gynäkologie,' 1886, s. 306.

already exist, they are increased both in strength and number. A subcutaneous injection of cornutine can induce premature labour in an animal without causing any ill-effects. Sphacelinic acid has a similar action, but the labour pains produced by it are of a tetanic character, and there are no intermissions, as is the case with cornutine. The fœtus consequently dies, or appears to be dead, more frequently than when cornutine is administered. Both preparations are amorphous—probably they have not yet been obtained in a pure state—and, if kept, gradually lose their efficacy and become altogether inert.

Favorable reports have been published as regards the application of cornutine on animals and human beings;[1] on the other hand, we have been warned against its use.[2] A quarter of a milligramme ($\frac{1}{270}$ of a grain) is said to be an efficient dose.[3]

Ergot is chiefly used in practice to stimulate and increase the contraction of the uterus, if delayed, after delivery, and thus to prevent all those complications which may arise from a lax state of this organ. The drug is also able to diminish and stop hæmorrhage from the non-pregnant uterus. Its use for the removal of fibroid growths and chronic hypertrophy of the uterus, rests, probably, on the assumption that it causes chronic anæmia in this organ.[4]

It is uncertain whether we can succeed in stopping hæmorrhage of the vessels of other internal organs by the subcutaneous injection of extract of ergot. That the vaso-constrictor centres and nerves—with the exception of those, of the uterus, in the spinal cord and in the uterus itself—can be stimulated by the drug is disputed.[5] We cannot conclude, merely from improvement taking place, that the good

[1] Erhard, 'Arch. f. Gynäkol.,' 1886, s. 309; L. Lewitzki, ibid., 1888, s. 121; ref. in 'St. Petersb. Dissert.,' 1887.

[2] M. Graefe, ibid., 1886, s. 529.

[3] Küstner, ibid., 1889, s. 565.

[4] G. Leopold, "Ueber den Wert der subcutanen Ergotininjection," u. s. w., 'Arch. f. Gynäkologie,' 1878, Bd. xiii, s. 182; P. Müller, 'Deutsche Zeitschr. f. Chirurgie,' 1884, Bd. xx, s. 15; Berthold, 'Centralb. f. Gynäk.,' 1895, s. 512.

[5] Hermanides, 'Berliner klin. Wochenschr.,' 1880, ss. 598 u. 617.

effect was caused by the remedy employed. I will not inquire further how far this is the case with regard to the treatment, with extract of ergot, of erysipelas or of that form of eczema which is supposed to arise from disturbed vascular innervation.[1]

The great variations which exist in the quality of ergot and its PREPARATIONS frequently brought the drug into disrepute. Not a few physicians discarded it, and altogether denied its utility. This is an error. Ergot, so long as a good sample can be obtained and the indications for its use are properly interpreted, is as reliable as any other recognised medicine. Let us examine it more closely.

We find the following in the German Pharmacopœia :— "On infusing ergot in ten parts of hot water its peculiar odour, which is neither ammoniacal nor rancid, will be developed." The meaning of this is clear. Ergot contains as much as 35 per cent. of fatty oil, which decomposes easily ; it further contains albumen and mucin, which may form ammonia. It is therefore evident that if such decompositions take place, the active ingredients cannot remain unchanged.

To avoid this the Pharmacopœia prescribes further, "Powdered ergot is not to be kept ready prepared ; it must be roughly powdered when wanted, and dispensed in that condition."

The reason for this is that the constituents which rapidly undergo change when exposed to the air, lose their strength far less quickly so long as they remain enclosed within their hard covering, and the air is excluded, than when they are kept on the shelves of the chemist and are constantly exposed to the air.[2] The extraction of the fatty matter previously to powdering the ergot was not of much use in keeping the ergot unchanged ; it has therefore been abandoned, and the above-mentioned direction put in its place.

Ergot which had been kept for over twelve months, had no influence at all on the uterus in any of the experiments made by Kobert on pregnant animals. It is apparently

[1] O. Witzel, 'Der nervöse Charakter des Ekzems und die Behandlung desselben mit Elecktricität und Ergotin,' Doctordiss., Berlin, 1879.

[2] S. Schaefer, 'Berl. klin. Wochenschr.,' 1881, s. 296.

impossible to distinguish ergot which is more than a year old from that which is quite fresh. Perhaps the COLOUR OF THE FRACTURE, when the grain is broken, may afford some indication, as fresh ergot is paler than that which has been kept. A medical man who frequently uses ergot in his practice must take care that it is obtained from a reliable source, and that it is not more than twelve months old. The drug which has lost its strength is worse than none, as it only deceives and causes delay in the time of danger. Twelve months is probably too long a period; ergot can only be relied upon within the first four months after the harvest.

Hot infusions or decoctions of ergot ought never to be made, as they are greasy and nauseous on account of the fatty oil in them.

The officinal EXTRACTUM SECALIS CORNUTI, now called ergotine in Germany, is a reddish-brown, thick mass, which forms a clear solution with water, and is prepared by extracting the drug with cold water, and subsequently precipitating the mucin, &c., by means of alcohol. Such an extract, if properly and freshly prepared, possesses the qualities of the recent drug, and is, among other methods of application, suitable for injections under the skin. These are, however, painful, and bring on ulceration if the solution, as may easily happen, is rendered cloudy by a growth of fungus. Some physicians only dissolve it in water immediately before injecting it; they then give doses of from 0·05—1 gramme ($\frac{3}{4}$—15 grains). Its use is said to be especially indicated in cases of acute hæmorrhage of the lungs, and its action is also said to be reliable, and even prophylactic.[1]

Some German accoucheurs[2] also consider it to be a serviceable preparation. It can only be so, however, if it has not been kept too long.

EXTRACTUM SECALIS CORNUTI FLUIDUM, liquid extract of ergot,[3] has been introduced lately into the Pharmacopœia.

[1] Driver, 'Berliner klin. Wochenschr.,' 1884, s. 466.

[2] Schroeder, Fritsch, and Winckel; see M. Graefe, loc. cit.

[3] Fluid extracts are so prepared that the weight of the extract corresponds closely to that of the dry and powdered drug used for the purpose. The method of preparation varies according as the pre-

It is prepared by adding a little dilute hydrochloric acid, and digesting the ergot with two parts of alcohol and one part of water; the liquid is reddish brown and clear.

The dose of powdered ergot is from 0·3 to 1 gramme (4½ to 15 grains), that of the fluid extract about 6 to 20 drops. I do not know of any exact method of determining the value or dosage of either of the extracts.[1]

Cases of acute poisoning by the liquid extract of ergot have been reported.[2]

A woman suffering from hæmoptysis, which occurred at the beginning of a catamenial period, took at one dose 5—6 grms. (80—100 minims) of the liquid extract. The hæmorrhage from the respiratory passages ceased, whilst menstruation continued unchanged. About nine hours after taking the drug the woman became prostrate, being seized with dull heavy pains in the abdomen, dryness of the throat, disagreeable sensations in the skin, oppression at the pit of the stomach, and dyspnœa. She was further troubled with impairment of vision, tinnitus, and formication accompanied by a sensation of cold and a loss of sensibility in the limbs, which began in their extremities. In addition to these symptoms there were isolated spasms and rigidity of the flexor muscles; the fingers were pressed against the palm of the hand; the pulse was small, infrequent, and regular; the temperature 36·4° C. (97·5° F.). Recovery took place in four days.

scribed menstruum contains glycerine or not. The active ingredients in these fluid extracts are said to keep well. They are, however, unreliable preparations if, during the evaporation or distillation of the liquids containing them, the temperature is not kept within certain low limits. It must, however, be admitted that they are less unreliable than the extracts made after the old fashion, whereby many of the active constituents of the drug were decomposed by the temperature of 100° C. used during the process of evaporation.

[1] For the latest experiments, and the bibliography for the last twenty-five years of *Secale cornutum*, see A. Grünfeld, in Kobert's 'Arbeit a. d. Pharmakol. Institut zu Dorpat,' 1892, viii, ss. 108—169.

[2] Debierre, 'Berlin. klin. Wochenschr.,' 1884, s. 441.

Ergotism is the term applied to an epidemic disease which is caused by the use of rye bread, or other food, containing ergot.[1] It was called *Ignis sacer, Ignis St. Antonii,* in the Middle Ages, records of the disease being traced back to that period.[2]

It is doubtful whether or not ergotism was known to the ancients. What the Romans described as *Ignis sacer* allows of other explanations. The first mention of it in Germany dates from January, 857,[3] when, according to the Xantener Annals, there raged on the Rhine "plaga magna vesicarum turgescentium in populo et detestabili putredine eos consumpsit, ita ut membra dissoluta ante mortem deciderent." In the year 922 there was a similar epidemic in the south of France and north of Spain, and one occurred in Paris and its neighbourhood in 944. Most of those who were attacked by it fled into churches and monasteries, and recovered there. At Paris the Cathedral of Notre Dame was in especial request.[4] Nearly every one who could obtain entrance there was healed. The Duke Hugo Capet provided food every day for the sick people assembled there, although their number sometimes exceeded six hundred. When those who were convalescent returned to their villages

[1] French *l'ergot* = spur, from its curved or nail-like figure.

[2] See C. B. Fuchs' 'Das heilige Feuer des Mittelalters;' Hecker's 'Annalen der ges. Heilkunde,' 1834, Bd. xxviii, ss. 1—81.

[3] According to Hirsch, 'Geograph. and Histor. Pathol.,' vol. ii, p. 204 (New Syd. Soc. transl., 1885), Gregor von Tours gives an account of an epidemic which occurred at Limoges as early as 591.

[4] "Regnante Ludovico fortissimo († 1137), Francorum rege, Philippi regis filio, flagellavit Dominus regnum Francorum, et membra, quæ miseri homines exhibuerant servire injustitiæ et iniquitati ad iniquitatem, cœpit morbus igneus consumere, quem physici sacrum ignem appellant. . . . Occurrunt morbo medici, artes et ingenia excitant, experimenta probant: sed hæc omnia reprobantur, quia digitus Dei erat, et non est consilium contra Dominum . . . deportaverunt infirmos suos, nec quantum de proximo, verum et de remotis partibus ad ecclesiam B. D. G. Mariæ in Parisia urbe sitam. . . . Tribus tamen exceptis omnes male habentes curati sunt . . . erant autem qui sani facti sunt numero centum . . . et turbatus fugit adversarius noster diabolus, non expectata virginis potestate," 'Acta Sanctorum,' 1643, vol. i, p. 151.

the "holy fire" again broke out, and was only extinguished by their return to the cathedral.

This went on for centuries. The disease affected people of all ages and of both sexes. The hands, feet, chest, and face were destroyed by it. No medicinal remedy was of any avail, the disease was a chastisement from God. Everybody who was attacked by it was racked with intolerable pain until death supervened, unless other than earthly remedies lessened their suffering. The disease was a wasting one, so that the flesh below the shrivelled and livid skin disappeared from the bones, whilst the sick people, their pain and smarting constantly increasing, felt the agony of death at every moment. Death, so eagerly longed for, however, came only when the "fire" had destroyed the limbs. It appeared wonderful that this "fire" was able to consume without heat, for the people affected by it became so icy cold that they could not be warmed in any possible way. If recovery set in, this coldness disappeared, and was replaced by an intolerable heat.

This form of the disease is named GANGRENOUS ergotism, in contradistinction to another form which is seen more in northern districts, and is called SPASMODIC ergotism. The former has almost entirely disappeared, owing to the removal or attenuation of the causes which produced it; whilst the latter still exists, and therefore interests us more closely.

Several centuries elapsed before it was discovered that this frightful disease arose from natural causes. It was noticed that it occurred always after a bad harvest, after a wet summer, and more particularly in moist districts, further that it disappeared as soon as the crops of such years had been consumed, and that it did not appear when the harvest was good. It was observed that recovery, or at any rate improvement, set in whenever the patient obtained different and wholesome bread, in consequence of his removal to some other place or owing to other circumstances; and it was also observed that the disease returned when the food of those who had partially recovered, was prepared with flour in which small black-looking pieces of ergot were visible.

Numerous observations have been made[1] in recent times,

[1] Th. O. Heusinger, 'Studien über den Ergotismus; aus Anlass

from which it appears that ergotism is essentially a disease of the nerves.[1]

The following is, in general terms, the view adopted by Menche and other writers:

In children the first poisonous symptoms often appear after they have eaten bread, containing ergot, for five days: all delicate people are taken ill immediately; strong adults often eat such bread for months before they become affected. Many symptoms have been observed, such as progressive weakness, headache, giddiness, vomiting, violent diarrhœa, and morbid appetite; then FORMICATION sets in, usually in the limbs alone, sometimes all over the body. It often happens that the latter symptom continues during the entire illness, so that we have it as the first characteristic symptom, as well as the last. Soon, however, we have contractions of the limbs, fingers, and toes, some of the extensor and some of the flexor muscles being affected. This occurs usually on both sides, and often gives rise to great pain; the pain is increased by passive extension. The duration of these contractions varies from a few minutes to several days; the intervals between them also vary considerably.

Griepenkerl had a case in which the abdominal muscles were so tense that they felt like a board, and at the same time were very sensitive. Frequently tenesmus and retention of urine are present. The feeling of want of breath, pain in the præcordial region, and the "globus" in the throat point to spasm of the diaphragm, and of the pharyngeal muscles. CLONIC CONVULSIONS are rare; they are chiefly of a co-ordinated character, such movements of the fingers as are seen when playing the piano, or of the arms when beating the drum. Sometimes they resemble those of chorea, and in the place of spasms of the flexor muscles, continued involuntary contractions of a varied character occur in almost all the muscles, even in those of the tongue and of the jaw, and are always accompanied by violent pain.

einer Epidemie in Oberhessen,' 1855–6, Marburg, 1856; O. Griepenkerl, 'Vierteljahrschr. f. ger. Med.,' 1858, Bd. xiii, s. 1; Leyden, 'Klinik d. Rückenmarkskr.,' 1875, ii, s. 287; H. Menche, 'Arch. f. klin. Med.,' 1879, Bd. xxiii, s. 246.

[1] Fr. Tuczek, 'Arch. f. Psychiatrie,' 1882, Bd. xiii, s. 99; Ungefug und Lentin, 'Vierteljahrschr. f. ger. Med.,' 1856, Bd. ix, s. 11.

In many abortive cases the contractions, which lasted for two or three weeks, were the only symptoms, but they were followed by a prolonged convalescence. The more severe cases ended in epilepsy and insanity.

There was no impairment of sensibility, and analgesia of the finger tips was only noticed in a few cases. The fingers in these cases were anæmic, and the epidermis was raised in large blisters, but there was no inflammation. The patients often lost the nails of all their fingers and toes simultaneously, as well as their hair. In one case the latter was associated with considerable ulceration of the scalp. Such shedding of the nails has been also mentioned several times by Heusinger. It was associated with the old "gangrenous ergotism." The perspiration was usually increased, but the catamenia were suppressed. Abortion—and this is very remarkable—did not occur, even although pregnant women were frequently, and often severely, attacked by the disease. Immunity to the poison could not be produced. It was precisely in the mild cases that relapses most frequently took place when the tainted bread was again eaten.

Sixty-five grains of ergot were administered to a badly nourished and enfeebled young woman during her labour. Six weeks afterwards mortification of all the limbs, the nose, and the ears set in.[1] Whether this condition which resulted in the loss of her limbs, was altogether due to the ergot is an open question; at any rate, it should make us cautious in using the drug.

The quantity of ergot in grain is naturally also extremely variable; as much as 25 per cent. has been found in rye (Griepenkerl, in the Duchy of Braunschweig, 1856). In this particular instance, in two small villages a relatively larger number of individuals were attacked than elsewhere, the numbers being forty-one and twenty-two, of whom altogether thirteen died.

Ergotism is not due merely to that constituent in ergot which is therapeutically important; it probably arises just as much from the so-called alkaloids—ergotine and ecboline—which it contains, for these also have been shown to have poisonous properties. To these, perhaps, should be added

[1] J. Begg, 'Lancet,' 1870, vol. ii, p. 397.

the putrefactive changes in rye flour which occur in wet and bad years, and to which the presence of ergot is said to contribute.[1] The alkaloids of putrefaction, the ptomaines, are recognised as poisons, and they may therefore very likely have something to do with the epidemics above mentioned. Further, a soft, pungent resin, with emetic properties, as well as leucine and trimethylamine, are said to exist in ergot. All these and other unknown substances may take part in giving rise to the changing picture of ergotism, from which, however, as far as we are concerned, two important symptoms stand out prominently, namely, the formication in the limbs, and the stimulation of the spinal cord which occurs at the commencement of the disease.

Naturally, in treating these cases, the first thing to be done is to remove the cause, and then by the administration of the usual narcotics to relieve the spasms, and the great pain resulting from them; to give mild aperients for the constipation which nearly always exists, and to relieve the spinal meningitis by local bloodletting, which, owing to the extreme tenderness both of the external and the internal parts, is much better done by means of leeches than by cupping.

Kobert has produced some of the symptoms of gangrenous ergotism by feeding different kinds of animals with SPHACELINIC ACID. In male fowls, amongst other symptoms, the comb and gills become dry and black in consequence of hyaline thrombi in the minute arteries, these thrombi being produced by the strong continuous contraction of the vessels. One bird lost both its wings after it had been fed on this acid for nine months. Similar necrotic changes to those in the comb were found in the spinal cord. Gangrenous vesicles were produced on both ears of a young pig. In rabbits parenchymatous hæmorrhage was set up in the stomach and bowels. Sphacelinic acid excites the vaso-motor centre in the medulla oblongata, and so raises the blood-pressure; in large doses it causes general convulsions.

[1] A. Pöhl, 'Polytechnisches Journal,' 1883, Bd. ccl, s. 324; 'Bericht der deutschen chem. Ges. in Berlin,' 1883, s. 1975.

A new drug has recently been introduced which has a similar action to ergot, viz. the rhizome of HYDRASTIS CANADENSIS, a North American plant belonging to the Natural Order *Ranunculaceæ*. The EXTRACTUM HYDRASTIS FLUIDUM of the German Pharmacopœia contains two alkaloids, hydrastine, $C_{21}H_{21}NO_6$, and BERBERINE, $C_{20}H_{17}NO_4 + 6H_2O$. The extract, given in doses of thirty to sixty drops, two or three times a day, contracts the vessels of the uterus without stimulating the muscular tissue of that organ, so that it is not adapted for the purposes of inducing labour, or of increasing the pains if labour has already begun.[1] It acts beneficially in hæmorrhages, tumours,[2] and inflammation of the uterus, especially in virgins. The vessels also of the other abdominal organs are made to contract by this drug, so that its action probably extends still further. The extract does not generally interfere with digestion, but rather tends to improve it.

Schatz,[3] who was the first in Germany to direct attention to hydrastis, subsequently stated that good results could only be obtained by using an extract which was made from FRESH roots grown in America, but not from one prepared, as in Germany, from the dried root; and, moreover, that the administration must be continued for several weeks.

More recently HYDRASTININE,[4] as the active constituent, has been recommended for use. It is an alkaloid with the formula $C_{11}H_{11}NO_2$, and is obtained by oxidising hydrastine with warm dilute nitric acid, so that it decomposes into hydrastinine and opianic acid, $C_{10}H_{10}O_5$. The hydrochlorate, which is easily soluble in water, is the preparation employed. In experiments upon animals it raises the blood-pressure by causing contraction of the blood-vessels. In large doses it kills by paralysing the central nervous system, for the heart does not seem to be affected, as it is by hydrastine. Again, hydrastinine is efficacious in cases of hæmorrhage from the uterus, when given in doses of 0·05

[1] Schatz, 'Berl. klin. Wochenschr.,' 1886, No. 19.

[2] V. Schmidt, 'Prager med. Wochenschr.,' 1887, No. 42.

[3] Schatz, 'Centralbl. f. Gynäkol.,' 1883, s. 686.

[4] For the bibliography of the subject consult E. Falk, 'Therap. Monatshefte,' 1890, s. 19; 'Arch. f. path. Anat.,' 1890, Bd. cxix, s. 399; also P. Marfori, 'Arch. f. exper. Path. u. Pharmak.,' 1890, Bd. xxvii, s. 161.

gramme ($\frac{9}{10}$ of a grain) to 0·1 gramme (1½ grains) daily, or when it is subcutaneously injected once or twice a week. The best results were obtained when it was given, in congestive dysmenorrhœa or in menorrhagia, six to eight days before menstruation was expected to commence.

In the Southern States of North America the BARK OF THE ROOT of the cotton plant, *Gossypium herbaceum*, is also used for the purpose of criminal abortion. This has led to the investigation of its action in stimulating contractions of the uterus, in place of ergot or hydrastis, in obstetrics, and in cases of hæmorrhage not connected with pregnancy.[1] A hot infusion of the drug has been given daily for months, either one dose of 10 grammes (150 grains) or two doses of 7·5 grammes (112 grains); or two teaspoonfuls of the fluid extract, in sweetened water, were given two or three times a day. The stomach, as a rule, tolerates it well.

Besides the three drugs already discussed which stimulate the uterus, I must mention another,[2] which is said to have a SEDATIVE effect on it, VIBURNUM PRUNIFOLIUM, plum-leaved snowball, belonging to the Natural Order *Caprifoliaceæ*, and also a native of North America. The extract prepared from the fresh ROOT-BARK is said to diminish labour pains arising during pregnancy and endangering its continuance. It should, therefore, be of use in cases of habitual abortion, when this does not arise either from some general disorder or particular local disease, such as syphilis, nephritis, &c. Its action is said to be greatly superior to that of morphine or bromide of potassium, which are usually given in such cases, although it often occurs that the former cannot be dispensed with at the commencement of the treatment. The best form in which to prescribe it is a teaspoonful of the thick extract mixed with an equal weight of diluted alcohol, twice daily. It must be given for a considerable period. In habitual dysmenorrhœa we must commence the administration of the drug ten to fourteen days before the period is expected.[3]

[1] Prochownik, 'Centralbl. f. Gynäkol.,' 1883, s. 647.

[2] Schatz, 'Centralb. f. Gynäkol.,' 1888, s. 394.

[3] Joseph, 'Deutsch. med. Wochenschr.,' 1892, s. 317.

XIII.

Calabar bean or ordeal bean—Salicylate of physostigmine—Wholesale poisoning by the beans—Experiments on animals—Explanation of the details—Use of physostigmine in ophthalmic surgery and in atony of the intestines—Pilocarpine—Its sudorific action—Other glands also affected—Other actions—Experiments on animals—Antagonism to atropine—Therapeutic use—Nicotine—Effects on animals—Experiments on individuals—Similarity of its action to that of pilocarpine—Tobacco leaves—Chemical researches on tobacco smoking—Its injurious and its beneficial effects—Some historical details about tobacco.

THE dark chocolate-brown seeds of *Physostigma venenosum*, belonging to the Natural Order *Papilionaceæ*, are somewhat similar to the common scarlet runner in appearance, and are used, in trial by ordeal, in some parts of Western Africa, to determine the innocence or guilt of persons accused of witchcraft, and other crimes. Attention was first drawn to the ordeal bean by Sir R. Christison[1] of Edinburgh in 1855, who had experimented with it upon himself to ascertain its poisonous qualities. Sharpey in 1858 experimented with it upon frogs, and its physiological action was subsequently examined more closely by Th. Fraser in 1862 and subsequent years.[2]

It is called Calabar bean because it was first found in Old Calabar, in the Gulf of Guinea.

The constituent which concerns us is the alkaloid PHYSOSTIGMINE, which is also known as eserine. It is officinal in Germany as *Physostigminum Salicylicum*[3] (salicylate of physo-

[1] R. Christison, "The Properties of the Ordeal Bean of Old Calabar," 'Edin. Month. Journ. of Med.,' 1855, March, p. 193.

[2] Th. Fraser, 'Lancet,' 1863, ii, p. 598; 'Trans. Roy. Soc. Edinb.,' 1872, vol. xxvi, pp. 529—713.

[3] Physostigmine is the preparation contained in the British Pharmacopœia.—TRANSL.

stigmine). This consists of colourless or slightly yellow, glistening crystals, which are soluble in 150 parts of water and in 12 parts of alcohol, and have a neutral reaction. The salt, if kept dry, remains unchanged for a long time, even on exposure to light, but its solution becomes red in a few hours. The presence of salicylic acid in the officinal salt has no medical significance; it merely forms a good crystalline compound with the alkaloid. The empirical formula for physostigmine, as determined by Hesse, is $C_{15}H_{21}N_3O_2$.

In the year 1864, at Liverpool, some Calabar beans, landed from a vessel which had arrived from Africa, got into the hands of the dock labourers' children, and were eaten under the impression that they were ordinary nuts. Within a few minutes no less than seventy children were taken ill, forty-six of whom were removed to the hospital and put under treatment.[1]

Considerable weakness of the muscles of a paralytic nature, lasting three days, was observed in the cases which recovered. Vomiting, diarrhœa, pain in stomach, contraction of the superficial arteries, were among the further symptoms. There was no loss of consciousness. The pupils were examined in fifteen cases, but were contracted in only three—a fact which corresponds with the action of atropine. Physostigmine only affects the iris with certainty when it is locally applied. A boy who had eaten six beans was moribund on arriving at the hospital. This was the only death. The other children recovered, having, as it happened, taken a smaller quantity on a full stomach, and then vomited soon afterwards.

I inject 0·0025 gramme physostigmine in 5 c.c. of water, under the skin of a small rabbit; in three minutes the animal becomes very restless; two minutes later it is paralysed, and six minutes after the injection is slightly convulsed and dies. MARKED FIBRILLAR CONTRACTIONS OF THE DORSAL MUSCLES ARE SEEN AFTER DEATH. The heart beats powerfully to the last, as is seen on rapidly opening the thorax.

[1] Cameron and Evans, 'Med. Times and Gazette,' 1864, p. 406; ref. 'N. Rep. d. Pharm.,' 1865, s. 79.

I put one drop of the above solution in the eye of another animal a few minutes ago, and you can now see that the PUPIL is greatly CONTRACTED ; indeed, it will soon be almost imperceptible. This takes place also in human beings, and is accompanied by dimness of vision, spasm of accommodation, and myopia.

If I develop the symptoms of poisoning more gradually, by injecting the above dose in the course of half an hour, we notice that the bowels are always strongly acted upon, and that the urine is generally voided. If we open the peritoneal cavity the whole INTESTINAL CANAL, including the stomach, is seen to be STRONGLY CONTRACTED AND ANÆMIC, at first only partially, rosary like, but later on more uniformly —the effect varying with the dose. At first there is strong peristalsis, but this movement eventually ceases. Before this an increased secretion of saliva and tears, and, if the animal is a cat, of sweat on the paws, is noticeable, whilst we also find that the secretion of mucus is increased if we make an internal examination.

Careful consideration of the effects produced, leads to the following conclusions :—Physostigmine paralyses the central nervous system ; the spinal cord and the medulla oblongata being most rapidly affected. According to the dose, this paralysis may be preceded by excitation, which is chiefly shown by more frequent and deeper respiration. Death is due to suffocation, but the convulsions developed by this cause are here only slight, as the spinal cord is paralysed. The excitation of the skeletal muscles, as shown by the fibrillar contraction, is due to their stimulation by the poison, for it takes place also when the nervous centres have been previously paralysed by chloral, or the motor nerves by curare, or when these nerves have been divided. The poison, therefore, probably acts only upon the muscular tissue.

It is probably also the muscle itself which is acted upon when the iris contracts. A pupil which has been made to contract by physostigmine will dilate a little if it is suddenly shaded ; it also dilates when the cervical sympathetic [1] is stimulated. Again, the contraction of the pupil is much

[1] Rossbach, ' Pharmakol. Untersuchungen,' Würzburg, 1873.

more strongly marked after an efficient application of physostigmine than it is after simple section of the sympathetic. It necessarily follows that the myosis is not due to a paralysis of the sympathetic which controls the dilator muscle, but to a stimulation of the endings of the oculo-motor nerve, or of the sphincter itself. The following considerations show that the sphincter itself is concerned :—atropine in moderate doses causes mydriasis, physostigmine removes this ; now atropine certainly paralyses the nerve-endings, but not the muscle of the iris when given in moderate doses, so that physostigmine can only influence the latter. Other myotic poisons which, as we know, act only on the nerves (muscarine, nicotine, pilocarpine), do not counteract the mydriasis which has been caused by atropine. Further, the fact that the pupil which has been caused to contract by physostigmine can be dilated with atropine, does not alter the argument, for now, the normal "tone" of the oculo-motor nerve-endings, upon which the contraction partly depends, is lost, just as it was when we suddenly shaded the eye.

Physostigmine increases the pressure in healthy eyes without previously diminishing it ; the pressure, however, falls subsequently. Physostigmine also lowers the ocular pressure in morbid conditions of the eye (glaucoma) by stimulating the muscular coat of the blood-vessels, and thereby modifying the circulation in this organ.[1]

The marked contraction and anæmia of the intestines depend also upon excitation of the non-striated muscle-fibres. The same holds good in the case of the spleen, bladder, and uterus. This effect upon the intestines is not diminished or increased by doses of atropine which are sufficiently large to produce paralysis of the nerves.

Further, the drug seems to affect the protoplasm of the glands, for on paralysing their nerves by atropine the increased secretion produced by the drug is not checked.[2]

It is natural that the PARALYSING EFFECT of physostigmine upon the spinal cord, which is developed before the sensorium

[1] Laqueur, 'Arch. f. Ophthalm.,' 1877, Bd. xxiii, iii, s. 149 ; 'Centralbl. f. d. med. Wiss.,' 1876, s. 421.

[2] Heidenhain, 'Arch. f. ges. Physiol.,' 1872, Bd. v, s. 309, und 1874, Bd. ix, s. 335.

is paralysed, should be made use of in all morbid conditions attended with irritability of the cord. Consequently preparations of Calabar bean have been tried, from 1864 to the present day, in a number of cases of this kind. Riess,[1] speaking from his own experience, says, "If we consider all these results, we must admit that they encourage us to use physostigmine to a larger extent than we have hitherto done, in order to diminish the irritability of the central nervous system in cases of chorea and various other nervous affections, which are accompanied by spasmodic muscular movements."

Calabar bean very quickly found a place in OCULAR THERAPEUTICS. A local application is here sufficient, and consequently there is little fear of poisonous effects being produced. Physostigmine has an opposite action to atropine, and produces a beneficial effect in many cases in which the use of the latter drug is contra-indicated.

The power of physostigmine to STIMULATE MUSCULAR TISSUE has further been proved in atony of the bowels with prolonged constipation and flatulence. Subbotin utilised, on human beings, the results of these experiments, which showed that the Calabar bean greatly diminishes the quantity of blood in the intestinal arteries, and causes violent tetanic contraction of the bowels, whether it is given subcutaneously or by the mouth.[2] Doses of 0·006 gramme (about $\frac{1}{10}$ of a grain) of the extract were sufficient to get rid of a fæcal accumulation in the colon which had followed a prolonged catarrh, and which purgatives, &c., had failed to relieve. This localised effect of physostigmine, in suitable cases, with the dose carefully adjusted, is produced without any unpleasant effects of the remedy showing themselves. This effect continues for two or three days after the administration of the drug.

[1] L. Riess, 'Berl. klin. Wochenschr.,' 1887, No. 22.

[2] F. Bauer, 'Centralbl. f. d. med. Wiss.,' 1866, s. 577; Subbotin, 'Arch. f. klin. Med.,' 1869, Bd. vi, s. 285; v. Bezold und Götz, 'Centralbl. f. d. med. Wiss.,' 1867, s. 241; S. Schaefer, "Extractum Fabæ Calabaricæ bei Atonie des Darmes," 'Berliner klin. Wochenschr.,' 1880, s. 725; Hiller, 'Deutsche med. Wochenschr.,' 1883, s. 123; W. Maschka, 'Berl. klin. Wochenschr.,' 1883, s. 227.

Veterinary surgeons have also corroborated these statements, and have utilised them, especially in the colic associated with constipation; 0·002 to 0·1 gramme ($\frac{1}{30}$ to 1½ grains) of physostigmine sulphate produces in twenty to forty minutes, after being injected subcutaneously, a vigorous action of the bowels with straining, the evacuations at first being hard, and afterwards thin and watery.[1]

Naturally the use of physostigmine in practice requires great care. The Pharmacopœia fixes the maximum single dose at 0·001 gramme ($\frac{1}{60}$ of a grain), and the largest quantity to be given in a day at 0·003 gramme ($\frac{1}{20}$ of a grain). If we commence with a fifth of these quantities we need scarcely fear any unpleasant effects. The use of the EXTRACTS is not recommended, because they do not keep well, and because of the presence of another alkaloid, calabarine, which has a similar action to that of strychnine.[2]

A young girl eight years old, suffering from chorea, had a subcutaneous injection given her, at the Berlin Charité, of 0·005 gramme ($\frac{1}{20}$ of a grain) of physostigmine. She was seized with violent vomiting, sweating, and salivation, diminished pulse-rate, contraction of the pupils, and prostration—symptoms which only yielded after several hours to administration of stimulants.[3]

In such cases the first remedy to be employed, for reasons already mentioned, is atropine. Fraser[4] has shown that in the case of animals it is possible, by means of atropine, to neutralise the effect of even three and a half times the minimum fatal dose of physostigmine.

[1] Möller, 'Tagebl. d. Vers. d. Naturf. und Aerzte,' 1882, s. 226; Fröhner, ref. in 'Fortschr. d. Med.,' 1884, s. 31; W. Wolff und L. Lewin, 'Deutsche med. Wochenschr.,' 1883, s. 149; Fröhner, 'Arzneimittellehre f. Thierärzte,' 1893, s. 191.

[2] Harnack, 'Arch. f. exper. Path. u. Pharmak.,' 1880, Bd. xii, s. 334.

[3] Ledderstaedt, 'Berlin. klin. Wochenschr.,' 1888, s. 336.

[4] Th. Fraser, loc. cit., p. 617.

In 1874 Cutinho, a Brazilian physician, introduced to the notice of the medical profession in Paris the leaves of *Pilocarpus pinnatifolius*, a shrub belonging to the Nat. Ord. Rutaceæ, and growing two or three metres high in his native country; it had been employed as a sudorific under the name of jaborandi. Experiments upon patients, carried out by Gubler and others, confirmed the fact that it possessed this property in a marked degree, even when no water was taken with it. This caused all the more sensation because, in accordance with modern scepticism, it was generally supposed that there was no remedy which possessed a direct sudorific action. If under the influence of drugs the skin became moist, this was due, so it was asserted, not to the remedy employed, but to the large quantity of hot water which was imbibed in the form of infusion of lime or elder flowers, and the simultaneous employment of blankets and feather beds.

At first only the leaves of jaborandi were experimented with, till Gerrard in London and Hardy in Paris isolated pilocarpine, $C_{11}H_{16}N_2O_2$, from them; the hydrochlorate of this is now officinal in Germany. The salt is white and crystalline, with a neutral reaction and bitter taste; it absorbs moisture from the air, and is readily soluble in water and alcohol.

We can study the very interesting action of pilocarpine best in human beings. It has been the subject of many observations.

The account given by Leyden and others[1] is much as follows:—A few minutes after a subcutaneous injection of 0·01 to 0·02 gramme ($\frac{1}{6}$ to $\frac{1}{3}$ grain) has been given, the face and forehead become red, the veins of the forehead are greatly swollen, whilst PERSPIRATION shows itself both here and over the entire body, and gradually becomes very profuse. The sweat is watery, odourless, slightly acid (from the presence of acid sebaceous matter), or neutral. A few minutes later the patient is bathed in perspiration, great beads appear on the forehead and

[1] Leyden, 'Berliner klin. Wochenschr.,' 1877, ss. 386 u. 404; E. Bardenhewer, ibid., 1877, s. 7; H. Curschmann, ibid., 1877, s. 353; A. Lösch, 'Arch. f. klin. Med.,' 1878, Bd. xxi, s. 259.

face, and trickle down in large quantities. The total loss of weight from the perspiration during an hour—so long does the action continue—has been estimated at 500—700 c.c. (about 1 lb. to 1½ lbs.).

In addition to this there is increased SALIVATION, commencing as soon as the secretion of perspiration, and lasting about the same length of time. In one instance salivation was so profuse that 550 c.c. of saliva, with a specific gravity of 1·005, were collected one hundred minutes after an injection of pilocarpine (Bardenhewer). There may be also an increased flow of tears; this, however, does not occur so constantly, nor is it so strongly marked. The tears either fall down the cheeks or pass down the nose. Further, the secretion of mucus in the trachea is increased, and is shown generally by expectoration. Finally there is usually an increased desire to micturate, and an abundant secretion of urine, but this condition soon passes off. The total quantity of urine passed in the twenty-four hours is diminished, owing to the great amount of water passing off in the perspiration and saliva.

With regard to the secretion in the RESPIRATORY PASSAGES, Rossbach[1] has found that such a copious flow of thin mucus is set up in the trachea and bronchi of dogs, that numerous rhonchi can be heard all over the animal's chest, and that great quantities of phlegm are driven into the trachea by the violent expiratory efforts of the animal.

Unpleasant and dangerous symptoms sometimes show themselves. In the first place we have great nausea and vomiting, which are followed by great exhaustion—conditions which are, however, not caused by cautious doses. The patient frequently then falls asleep, and wakes up invigorated and refreshed. These effects not infrequently continue for some days, and often, especially in people who are feeble and pulled down, dangerous collapse, associated with cardiac weakness, is set up, even in the earlier stages.

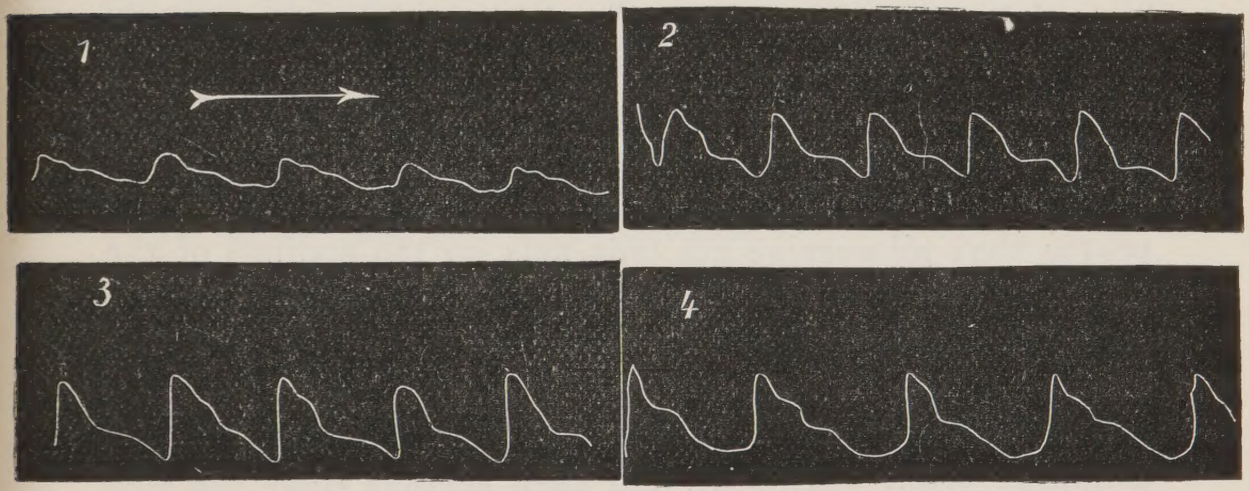
Dimness of vision is often developed. This is so marked in many cases that large print cannot be read at a distance of 16 cm. (about 6 inches), although it is read without any difficulty by the patient under ordinary circumstances.

[1] Rossbach, 'Festschrift,' Würzburg, 1882, s. 43.

This is not due to suffusion of tears, for it also takes place when the flow has ceased.

The VESSELS OF THE SKIN are dilated. The temporal arteries, for instance, which before were hardly visible, stand out prominently and pulsate visibly. The veins of the forehead also become turgid ; a similar dilatation of the radial artery is perceptible to the touch, and the veins of the limbs frequently appear to be swollen. The pulse becomes more frequent, naturally not to any great extent, rising perhaps from 80 to 100. A diminution in its rate has not been observed with medicinal doses of pilocarpine. Here are some sphygmographic tracings taken by Leyden :

FIG. 26.



No. 1 is the normal pulse ; No. 4 was taken sixteen minutes after the injection was given. The change may last for an hour.

The temperature is not much affected in human beings by pilocarpine. In some cases it rises slightly at first, 0·1° to 0·5° C. (0·2° to 0·9° Fahr.) ; in others there is no change, or at most a slow insignificant drop of one tenth of a degree or so, which frequently lasts till the following day. This is in the first place due to the cooling of the skin which results from the larger supply of blood, and the increased evaporation of water. Corresponding with these conditions the temperature of the skin is slightly increased at first, when it is full of blood, whilst later on it may fall 0·5° (about 1° Fahr.), owing to evaporation.

Nearly all this has been closely examined in animals.[1]

A horse received an injection of 0·4 gramme of pilocarpine under the skin of the back. Salivation ensued in three minutes, and lasted for several hours; two minutes later PERSPIRATION SHOWED ITSELF AROUND THE POINT OF INJECTION, and then became more profuse and general, but was not universal until nineteen minutes later. The perspiration of the paws of cats depends upon the sciatic nerve. It is a true secretion; we can readily develop it by stimulating the divided nerve. We can also do so by injecting the same leg with pilocarpine. In both cases the alkaloid clearly is able to cause the secretion of sweat independently of the central nervous system. It can no longer do so when the peripheral nerve, having by section been separated for several days from its centre, is beginning to degenerate. If we ligature the arteries passing to the periphery, so that the pilocarpine cannot get to the nerve-endings or come in contact with the trunk of the nerve, perspiration can still be developed in the paws by the use of pilocarpine. This proves that pilocarpine not only acts on the endings of the sweat nerves, but that it has a specific action upon the centres which control the secretion of sweat (Marmé).

The dilatation of the vessels seems to depend upon the peripheral action of pilocarpine, for, like perspiration, this condition often begins at, and then spreads from, the spot where the puncture has been made; paralysis of the vaso-motor centre only takes place when a dose has been given which is far in excess of what is necessary to produce the sudorific effect of the remedy.

The secretion of SALIVA depends upon similar conditions to those which give rise to perspiration. If the nerves in connection with the glands are divided, and an injection of pilocarpine subsequently given, salivation is greatly increased (Carville). Pilocarpine must, therefore, act upon the gland tissue or the endings of the nerves. It can cause salivation, when the blood-supply of the glands is cut off, so long

[1] For the literature of the subject up to 1880 see Harnack und Meyer, 'Arch. f. exper. Path. und Pharmak.,' Bd. xii, s. 398; also Vulpian, 'Cours de Pathologie expérimentale,' &c., Paris, 1881, pp. 53—192.

as the cervical sympathetic remains intact; if this nerve is divided, then salivation does not take place. The alkaloid can, therefore, stimulate the glands by acting upon the salivary centre in the medulla oblongata (Marmé).

Injections of pilocarpine always cause distinct LACHRYMATION, even if the nervus lachrymalis, the nervus subcutaneus malæ, and the corresponding branch of the sympathetic in the neck are divided. As the secretion of tears is dependent upon the action of these three nerves, this experiment shows clearly that pilocarpine acts directly on their nerve-endings. Lachrymation is also produced, however, when the four large arteries in the neck are ligatured, so that the pilocarpine is prevented from coming in contact with the lachrymal glands. This shows that pilocarpine also acts directly on the centre for lachrymation.

I have already referred to the increased secretion of mucus which takes place in the bronchi of animals; it can also be proved that an increase in the secretion of cerumen is produced by the remedy: that it causes an increase in the secretion of milk is at least doubtful.[1]

Pilocarpine stimulates the peristaltic movement of the bowels by directly stimulating the solar plexus, and larger doses increase the intestinal secretions. It can be shown by previously ligaturing the large arteries of the neck, and dividing the two vagi, that these results are independent of any effect upon the brain. The muscular coat of the intestines is not affected by pilocarpine, for if we previously paralyse the solar plexus by atropine, pilocarpine produces no effect, although the intestinal muscular fibres still contract strongly when stimulated by electricity.

Vulpian has also observed an increase in the secretion from the stomach, the pancreas, the liver, and the kidneys after injecting this alkaloid. Contractions of the uterus have also been noticed; these are, however, slight and transient, at least in the human subject.[2]

Transitory contraction of the pupil, accompanied by simultaneous spasm of accommodation, has been sometimes

[1] F. Hamerbacher, 'Arch. f. ges. Physiologie,' 1884, Bd. xxxiii, s. 228; Strumpf, 'Arch. f. klin. Med.,' 1881, Bd. xxx, s. 263.

[2] P. Müller, 'Verhandl. d. phys. med. Ges.,' Würzburg, Bd. xiv.

observed in warm-blooded animals, as an effect of the remedy. These symptoms are prevented by the previous use of atropine, and, if present, disappear on its application. This proves that the action of pilocarpine does not resemble that of physostigmine, and that there is no direct stimulation of the sphincter muscle, nor any paralysis of the nerves which cause dilatation of the pupil, but, on the contrary, a stimulation of those causing contraction—that is to say, the endings of the oculo-motor nerve.

The ANTAGONISM between pilocarpine and atropine is very distinct. It is seen everywhere. All the secretions mentioned as being augmented by pilocarpine are checked by the subsequent administration of atropine; the pulse, if it has been diminished in frequency by pilocarpine, rises above the normal, the pupil dilates, and the intestinal evacuations cease. And, what is still more remarkable, a double antagonism exists,—in other words, that alkaloid gains the upper hand which is given in the largest quantity, so that after the one alkaloid has counteracted the effect of the other, the latter, if again administered, will counteract the excess of action which may be produced by the former.[1]

Pilocarpine has been tried therapeutically in all those cases in which, according to the former views on medical treatment, copious diaphoresis was indicated. The occasions for it are so numerous and so varied, that we shall have to leave the question of its employment in the various diseases to be discussed by your clinical instructors. The abundant secretion of saliva and mucus from the *primæ viæ*, resulting from the use of pilocarpine, is said to be of service in the removal of false membranes in croup, and of infectious matter in diphtheria and syphilis.[2] Deficient secretion of saliva or of gastric juice is said to be rectified by an infusion of jaborandi leaves (3—150).[3] Pilocarpine may act as an expectorant by liquefying the viscid secretions which

[1] Luchsinger, 'Arch. f. ges. Phys.,' Bd. xv, s. 486, und Bd. xviii, s. 501; Langley, 'Journ. of Anat. and Physiol.,' Cambridge, 1876, vol. xi, p. 173.

[2] G. Lewin, 'Charité-Annal.,' 1880, Bd. v, ss. 489—563 (with a considerable bibliography).

[3] G. Sticker, 'Sammlung klin. Vorträge,' 1887, No. 297.

accumulate in, and so block up, the air-passages.[1] With incautious doses this liquefaction or excessive watery secretion may give rise to dangerous œdema of the lung.

The antagonism between this drug and atropine, which is shown by their action on the glands and on some of the nerves, has been utilised in the treatment of cases of poisoning by the latter substance. As, however, the chief danger in these cases arises from the violent cerebral excitement, and as pilocarpine possesses no sedative action on the nervous system, we had better trust to morphine.

Various skin diseases have been treated successfully by subcutaneous injections of pilocarpine, such as extensive chronic eczema with induration of the skin and violent itching.[2] A dose of 0·01 gramme ($\frac{1}{6}$ of a grain) was given twice a day.

An interesting point was noticed in two patients who were treated with subcutaneous injections of pilocarpine for an affection of the eye. The hair on the scalp grew in a remarkable manner whilst they were under treatment.[3] That this may result from the drug is confirmed, in some measure, by the fact that the same unusual growth of hair has been noticed several times in animals, to which injections of pilocarpine have been given for other reasons. In one case a quantity of small fine hairs appeared in a bald place a few days after two subcutaneous injections.[4] I do not know whether these statements have received any further confirmation. At any rate, such a thing is conceivable on account of the stimulating effect which pilocarpine has upon the skin.

We must not lose sight, in administering pilocarpine, of its effects on the circulation, and on the intestinal canal. If disease exists in both these systems, the symptoms may be seriously aggravated.[5] An overdose causes death by paralysing the lungs, the secretion accumulating and blocking up the alveoli.

[1] Riess, 'Berl. klin. Wochenschr.,' 1887, No. 15.
[2] R. M. Simon, 'Brit. Med. Journ.,' 1892, February 6th
[3] G. Schmitz, 'Berl. klin. Wochenschr.,' 1879, No. 4.
[4] Schüller, 'Arch. f. exper. Path. u. Pharmak.,' 1879, Bd. xi, s. 88.
[5] Fuhrmann, 'Wien. med. Wochenschr.,' 1890, No. 34.

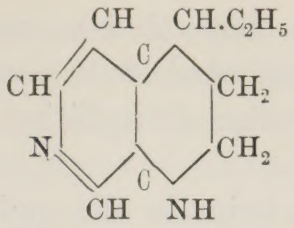
The officinal preparations are the leaves, FOLIA JABORANDI, and the salicylate of physostigmine, which has been already discussed. The maximum dose of the latter is 0·02 gramme ($\frac{3}{10}$ of a grain), and the largest quantity which may be taken in a day 0·05 gramme ($\frac{7}{10}$ of a grain).

Pilocarpine is easily decomposed. It is partially resolved into other bases, if an acid solution of it is evaporated down;[1] and it is owing to the presence of these bases, in the commercial physostigmine, that the drug appears to be uncertain in its action, and is regarded in such a different light by different physicians.

The action of NICOTINE is very similar to that of pilocarpine.

This alkaloid is obtained from tobacco (*Nicotiana tabacum, N. rustica,* &c.), a plant belonging to the Natural Order Solanaceæ, indigenous to America. The leaves are macerated with water, and boiled; the liquid is concentrated, rendered alkaline with lime, and then distilled. The distillate is concentrated, and the nicotine extracted by agitation with ether. The quantity of nicotine in tobacco varies greatly; in the dried leaves from 0·6 to nearly 5 per cent. has been found. It is a colourless or pale yellow, transparent, thin and oily fluid, and has an acrid odour and a pungent taste; it mixes readily with water, alcohol, ether, and fatty oils, has a strong alkaline reaction, and forms salts which crystallise with difficulty and decompose readily. Its formula is $C_{10}H_{14}N_2$. It was first prepared in a pure form by Reimann and Posselt in 1828. Its constitution may, perhaps, be represented by the following formula:

[1] Harnack und H. Meyer, loc. cit., s. 366; 'Annalen der Chemie,' 1880, Bd. cciv, s. 67, und 1887, Bd. ccxxxviii, s. 228.



This body presents some analogy to conine, which is also a liquid and is free from oxygen. Nicotine, like conine soon oxidises when exposed to air, becoming dark brown, cloudy, and resinous. Soon after the discovery of nicotine its poisonous properties were investigated by Orfila and others. A case of poisoning from it at Brussels, in 1851, which ended fatally, and caused a great sensation, first led to its action being thoroughly investigated.

I will now experimentally demonstrate the special symptoms of poisoning by this alkaloid.

I inject subcutaneously 0·001 gramme of nicotine, dissolved in water, into the back of a healthy frog. The animal soon becomes quiet. Its whole body is covered with moisture. When placed on its back it remains in that position, the eyes are closed, the head droops, and respiration has ceased. The fore-legs are stiff and drawn up to the body, the thighs are at right angles to the trunk, the legs are so drawn up by the spasm that the tarsi touch the pelvis; if the legs are forcibly extended they return at once to their former position; fibrillar contractions in different muscles can be seen through the uninjured skin. The toes are spread open and are rigid, and the web between them is put on the stretch. There is no increase in the reflexes. If I shake the board on which the creature rests, the spasms are not increased.

The frequency of the heart's action is at first diminished, owing to stimulation of the vagus; but as this nerve is subsequently paralysed, the action soon becomes normal. Stimulation of either of the vagi no longer stops, or even diminishes the heart's action. The excito-motor system is so little influenced that after the lapse of over an hour I can still count 40—50 strong pulsations a minute. The heart, however, will eventually succumb to the general paralysis, which is now beginning to show itself. The spasmodic rigidity of the limbs is replaced by relaxation; the exposed

sciatic nerve reacts but slowly, and a freshly exposed section of the spinal cord will soon respond as slightly. Only the direct muscular irritability lasts for any length of time.

In warm-blooded animals the poisoning process runs a very tumultuous course. The symptoms are extreme excitement and dread, loss of consciousness, trembling in the limbs, violent attempts to move but inability to do so, together with a want of co-ordinating power, sudden collapse, clonic spasms, tetanus, and failure of respiration—all this, as you see here in a rabbit, within a minute after a subcutaneous injection of one drop of chemically pure nicotine in 1 c.c. of water. The same symptoms are observed after the injections of a drop of nicotine into the jugular vein. The convulsions then set in within a few seconds, and death takes place half a minute later. After death the sciatic nerve, the brachial plexus, and the phrenic nerve react but slightly. If the other sciatic nerve had previously been divided, it would have retained its excitability for a longer time. This shows that the paralysis in the uncut nerve proceeds from the centre. The paralysis of the peripheral end of the nerve is also brought about through the blood, as is evident by the fact that the excitability of the sciatic in the frog lasts longer, if the artery, leading to it, has previously been ligatured.[1]

In the human subject, too, nicotine proves to be one of the strongest poisons. Dworzak and Heinrich, two medical students of Vienna, were induced by the elder Schroff, to take from 0·001—0·004 gramme ($\frac{1}{66}$ to $\frac{1}{16}$ of a grain) of the alkaloid, diluted with about 4 c.c. of water (about a drachm). Great excitement was experienced at first, and was soon followed by exhaustion, heaviness in the limbs, giddiness, unusual languor, and stupor. Later on, clonic spasms supervened, and lasted for about two hours. The limbs began to shake ; this movement spread to the trunk, until at last the whole body shook violently. The respiratory muscles were the most affected, the breathing was heavy and laboured, whilst each inspiration and expiration consisted of a series of short, jerky movements. A restless, sleepless

[1] Kölliker, ' Arch. f. path. Anat.,' 1856, Bd. x, s. 256.

night followed; the general disorder of the nervous system, the stomach, and intestines lasted the whole of the following day; even on the third day, though the second night was passed quietly, the symptoms of poisoning had not altogether disappeared. All this was the effect of only 4 mg. of nicotine!

I pass over any analysis of these symptoms, and especially any discussion as to the action on the various organs. These points are interesting purely from a toxicological point of view.

The FOLIA NICOTIANÆ, the dried leaves of *Nicotiana tabacum*, are officinal; nicotine is not. The leaves are used in veterinary therapeutics. Formerly they were prescribed in obstruction of the bowels, in strangulated hernia, and in extreme flatulent distension of the intestines. For this purpose an infusion containing 0·2 to 0·4 gramme (3 to 6 grains) was given as an enema. The use of tobacco in such cases (in which, however, physostigmine is much to be preferred) can be explained theoretically by what has been already said regarding the action of nicotine upon the intestines. The drug causes the latter, as well as the uterus, to contract, and the action may be so great as to give rise to genuine tetanus with great narrowing of the lumen. This is due to some stimulating effect produced locally, possibly on the ganglia.

Poisoning is rarely caused by pure nicotine, but frequently results from tobacco leaves. This is due to the careless use of tobacco infusions in enemas, to accidental swallowing of tobacco leaves, or to their accidental presence in some beverage; cases of poisoning through carrying tobacco leaves next the skin for smuggling purposes are said to have occurred.[1] Nicotine has, it is true, the high boiling-point of 247° C., but it evaporates easily at a very low temperature, and dissolves readily in water; sufficient may be absorbed in this way by the warm and moist skin to develop even poisonous symptoms.

[1] v. Hildenbrand, 'Journ. d. prakt. Heilk.,' 1801, Bd. xiii, s. 151; Namias, 'Gaz. des Hôpit.,' 1864, s. 461.

It is of greater importance to determine what influence TOBACCO SMOKING has upon the health. In order to do so we must ascertain first what substances smoke contains, and which of them pass into the blood. Several reports have been written on this subject.[1] The tobacco smoke was drawn through an aspirator, was first cooled and then absorbed by distilled water, spirit of wine, dilute sulphuric acid, and dilute caustic potash. The different products of the dry distillation of tobacco—for this is what smoking essentially is—were in this way absorbed in the different solutions, and their nature and amount determined.

First, does nicotine pass over in the smoke without undergoing decomposition ?

Two authorities have answered this in the negative. They say that the nicotine is decomposed by the heat and volatilised in such a manner that the smoke contains no trace of it ; that substances are formed from it which belong to the pyridine series of bases, C_5H_5N, and that these cause the well-known poisonous effects of tobacco smoking. These statements were important as they appeared to prove that this most active poison was not present in tobacco smoke.

Further experimental investigation led to another result. Experiments on animals with what was absorbed by the various solutions, showed the characteristic symptoms of poisoning from nicotine. This substance was chiefly found in the Liebig's condenser ; six to eight drops of its contents were sufficient to produce in a large frog violent spasms, general paralysis, and death—symptoms previously described as due to nicotine. v. Gorup-Bezancz has also demonstrated, by chemical means, the presence of nicotine in tobacco fumes. It must, moreover, not be forgotten that nicotine is very soluble in water, and that water is one of the products of the ignition of the tobacco, just as it is of the combustion of any other substance which contains hydrogen. The moist and hot smoke, drawn through a cigar or through ordinary tobacco, must necessarily become impregnated

[1] Vohl und Eulenberg, 'Vierteljahrsschrift f. gerichtl. Med.,' 1871, Bd. xiv, s. 249 ; E. Heubel, 'Centralbl. f. med. Wissensch.,' 1872, s. 641 ; F. Vas, 'Arch. f. exper. Path. u. Pharmak.,' 1894, Bd. xxxiii, s. 141.

with the nicotine contained in the tobacco over which it passes, and so carry the poison to the saliva and inspired air. Consequently, though all the nicotine may be decomposed at the spot where the tobacco is actually alight, the smoke takes up quite sufficient of it in passing through the rest of the tobacco.

There can be no doubt as to the presence in tobacco smoke, in distinct quantities, of bases derived from nicotine and belonging to the pyridine series. These bodies, the formula for which is $C_nH_{2n-5}N$, are oily volatile liquids, colourless at first, but afterwards becoming brown, and having a strong and peculiar odour. They are called—commencing with the lowest member of the series—pyridine, picoline, lutidine, collidine, parvuline, &c., and form the main ingredients of the former officinal Oleum Animale Fœtidum or Oleum Animale Dippelin (Dippel's oil). As this indicates, they are products of the dry distillation of animal refuse, and are formed by the decomposition of animal or vegetable matters containing nitrogen. Very likely some of the bases belonging to the chinoline series are also present in tobacco smoke.

Eulenberg has already demonstrated the action of the pyridine bases on animals, and his statements have been generally confirmed by other investigators.[1] The effects produced, were stimulation of the medulla oblongata giving rise to spasms of the whole body, and stimulation of the spinal cord and of the motorial end-plates of the nerves, which were soon followed by general paralysis. On mucous membranes these bases acted like caustics.

The poisonous nature of the products of the dry distillation of nitrogenous tissue explains why leaves which contain no nicotine cause nausea, paleness, vomiting, diarrhœa, palpitation of the heart, &c., when they are smoked.

Cyanogen in form of a metallic cyanide is also present in tobacco smoke, as may be easily demonstrated. I have in this test-glass a little water which has been made alkaline with ONE drop of caustic soda, and shaken up with some

[1] McKendrick und Dewar, 'Ber. d. d. chem. Ges.,' 1874, s. 1458; Harnack und H. Meyer, 'Arch. f. exper. Path. u. Pharmak.,' 1880, Bd. xii, s. 394.

smoke from a cigar. I add a few crystals of picric acid ($C_6H_2(NO_2)_3.OH$), and then warm it. The fluid at once turns a beautiful red, owing to the presence of the potassium salt of isopurpuric acid ($C_8H_5N_5O_6$)—a characteristic test for a cyanide. The presence of cyanides is also shown by other methods.[1] The great sensitiveness of the above tests suffices to show the presence of extremely small quantities of the cyanides. All the ill-effects produced by tobacco smoking can be explained by the presence of nicotine and of the pyridine bases; the presence of traces of cyanides is therefore of little importance.

A sulphocyanide, probably $NH_4.S.Cy$, is also present. Its presence is shown by passing the smoke through an alcoholic, almost colourless, acidulated solution of ferric chloride; this it turns bright red, owing to the production of ferric thiocyanide. This test also is extremely delicate. Cyanogen when combined with sulphur is not nearly so poisonous as it is when combined with a metal.[2]

The other known constituents of tobacco smoke have little pharmacological importance. They are ammonia, carbonic acid, the lower fatty acids, some unknown aromatic bodies, &c. Either they are indifferent, or their quantity and poisoning properties are of no importance as compared with nicotine and the pyridine bases. Tobacco smoke has a strongly alkaline reaction; thus if we blow it a few times upon moistened light blue litmus paper, spread on a porcelain plate, the colour is almost immediately changed to a dark blue.

Excessive smoking has often led to the following constitutional derangements:

I. Chronic hyperæmia of the primæ viæ with its usual sequelæ, imperfect gastric digestion being one of the most marked.

II. Irregular action of the heart, and disturbance of the nervous system, together with all the symptoms of general want of tone, hypochondriasis, tremor of the muscles, a sensation of numbness in the limbs, impeded respiration, angina

[1] A. Vogel, 'Repertorium f. Pharmacie,' 1869, Bd. xviii, s. 25.

[2] Podcopaew, 'Arch. f. path. Anat.,' 1865, Bd. xxxiii, s. 513; Paschkis, 'Wiener med. Jahrb.,' 1885, s. 531.

pectoris, neuralgia, hyperæsthesia, feebleness, dizziness.[1] These protean-like conditions may result in a serious nervous disorder, namely—

III. Amblyopia toxica, nicotic amblyopia, dimness of vision.[2] This was noticed by Mackenzie in England in 1835, but was more accurately observed by Hutchinson in 1864, and in 1868 was exhaustively discussed in Germany by Förster. It is an affection of the nervous connections of the visual apparatus, probably commencing paralysis of the optic nerve itself, and fortunately can be cured at its commencement by relinquishing smoking. A great number of such cases of tobacco amblyopia have been observed. The following case was reported to me, the details of which I think are particularly instructive.[3]

A man fifty-seven years old, and previously healthy, had never had any trouble with his eyes. He had lived half his life in North America, and had contracted there the habit of smoking fifteen large havanna cigars a day. He also spent a considerable time in his room, fed well, and drank a moderate amount of wine. In March, 1880, he first began to complain of an increasing weakness of his sight; this became so marked within five months, that he could not discern the large letters in the heading of the *Kölnische Zeitung*. No change in the eyes was observed except moderate hyperæmia of the choroid and CONTRACTION OF THE PUPILS, which, however, reacted equally. White letters upon a black ground were distinguished twice as readily as black ones upon a white ground. His general health, with the exception of frequent gastric catarrh, occasional migraine, and want of sleep, was undisturbed. After Prof. Saemisch had diagnosed the condition as nicotism of the optic nerves, the patient reduced his daily allowance of cigars to three, and then stopped smoking entirely for a

[1] Individual cases have been recorded by Siebert, 'Diagnostik d. Unterleibskrankh.,' 1855, s. 99, "Spinalirritation und Mesenterialneuralgie durch Cigarrenvergiftung;" L. Schotten, 'Arch. f. path. Anat.,' 1868, Bd. xliv, s. 172; Schauenstein, in 'Maschka's Handbuch,' 1882, s. 464; and by others.

[2] Filehne, 'Arch. f. Ophthalmol.,' 1885, Bd. xxxi, ii, s. 1.

[3] Communicated by letter from Prof. Finkelnburg.

few weeks; under this complete abstention a very marked improvement in his eyesight at once took place, and continued steadily. In a few months, however, there was a relapse, owing to the patient again smoking excessively. From the end of 1880 he smoked three to four cigars a day of the so-called nicotine-free variety, but in which the nicotine is only reduced, by a patent process, to a quarter or one third of the normal amount. His condition began to improve slowly but steadily, so that in the beginning of 1882 he was again able to read the text of a newspaper without spectacles. Beyond limiting the amount of tobacco, and taking more exercise in the open air, the patient made no change in his mode of living or diet.

Differing from most or perhaps all other chronic toxic conditions, nicotism, according to Finkelnburg's experience, is peculiar in this, that persons in whom it has once been developed—the particular form is immaterial—BECOME MORE SUSCEPTIBLE to the poisonous action of nicotine, at any rate for several years, so that a smaller quantity of tobacco will reproduce the toxic symptoms.

The length of time which elapses before all these chronic injurious results of tobacco smoking which I have just described are experienced, varies with the amount of nicotine that the tobacco contains. The acute cases are readily produced if, in consequence of an insufficient draw (that is access of air to the ignited portion), the nicotine is imperfectly burnt, and if, moreover, the amount of the final products of combustion—carbonic acid, water, ammonium salts, &c.—is too small, whilst, on the other hand, the amount of the intermediate products, such as pyridine, in the smoke is too large.

The following BENEFICIAL EFFECTS are mentioned as resulting from tobacco smoking—stimulation of the brain, the medulla, and the heart, with increased activity of these organs; increased peristalsis, and consequently more satisfactory evacuation of the bowels in cases where there is a tendency to constipation. The feeling of hunger is deadened, a fact which must often be of importance in certain vocations.

The rapidity with which people become accustomed to

this active poison is well known. It is very remarkable, and we cannot at present offer any explanation of it.

Tobacco used for chewing or snuff, owing to the way it is prepared, contains considerably less nicotine than tobacco which is used for smoking, and the nicotine does not pass into the circulation so readily when the tobacco is used in these ways.

The civilised world learned the use of tobacco from the savages of America—Columbus and his successors found the Indians smoking. The name tobacco is said to be of Indian origin ; the term nicotiana was given in honour of Jean Nicot, who was French Ambassador at Lisbon about 1560. He received some tobacco seed from a friend who had returned from America, and planted it in his garden. He praised and spread the fame of the leaves as a specific against all kinds of external troubles. The use of snuff for headaches was introduced by Catharine de Medici at the French Court.[1]

The plant became known in other countries in the meantime, and in the middle of the seventeenth century its use had spread to almost every country. A reaction against it arose in various quarters. Chief among the opponents to its use was James I of England, who published in London, in 1603, a pamphlet from his own pen, entitled "Misocapnus (καπνός = smoke) seu de abusu Tabaci Lusus regius."[2] The Czar Michael, a few decades later, punished his soldiers for smoking, with the knout and the rack, and when the offence was repeated, by slitting up the nose, and exile to Siberia. Urban VIII forbade the clergy and the Spanish laity of both sexes to use tobacco in either of its three forms[3] in the churches or porches during divine

[1] F. Tiedemann, 'Geschichte des Tabaks und anderer ähnlicher Genussmittel,' 1854, s. 137.

[2] One sentence runs thus: "O cives, si quis pudor, rem insanam abjicite, ortam ex ignominia, receptam errore, frequentatam stultitia: unde et ira numinis accenditur, corporis sanitas alteritur, res familiaris arroditur, dignitas gentis senescit domi, vilescit foris; rem usu turpem, olfactu insuavem, cerebro noxiam, pulmonibus damnosam, et si dicere liceat atri fumi nebulis tartareos vapores proxime repræsentantem!"

[3] The "pinch" is not the only form which is forbidden, as F. Tiedemann states; the original text expressly mentions "qui ore vel

service, under the penalty of excommunication. While reading Mass even—so runs his apostolical brief of January 30th, 1642—the priests chewed tobacco; they contaminated the holy vestments with their expectoration, and poisoned the church with its odious smell. Within this limited circle the restriction was effectual. But beyond, neither the royal book, nor the knout of the Czar, nor the papal proclamation against the enjoyment of tobacco as a "pravus usus" availed much. Pope Innocent X repeated, in 1650, this prohibition with respect to the Church of St. Peter in Rome, but Benedict XIII rescinded it in the year 1724. It is said that he did this because he was an inveterate snuff-taker, and was unable to refrain from dosing his nose with tobacco in church. This decree, a copy of which I have before me, orders absolutely, that the use of tobacco in the Church of St. Peter must not cause the least disturbance; smoking was consequently excluded, though it was allowed by the wording of the decree. The use of snuff is permitted in Catholic churches to this day.

naribus aut fumo per tubulos tabaccum sumere audeant vel præsumant."

XIV.

Strychnine—Nux vomica—Experiments on animals—Discussion thereon—Action of small doses on healthy individuals—Therapeutic application—Poisonous effects of strychnine—Brucine—The preparations of ammonium—Stimulating effect on the brain and spinal cord, ending in convulsions—Improvement of blood-pressure and respiration—The different preparations.

In small doses strychnine acts as a tonic on certain nerves, but in large ones it is a most powerful poison, causing convulsions.

Strychnos nux-vomica is a small East Indian tree belonging to the Nat. Ord. Loganiaceæ. Its fruit contains very hard, circular, and nearly flat seeds, which are covered with soft silky hair. By soaking the seed in water, the horny albumen or endosperm readily splits into two halves free from starch. Its taste is very bitter, owing to the presence of two alkaloids, strychnine and brucine. As much as 2·5 to 4 per cent. of these two alkaloids have been found in the seed. The former has the formula $C_{20}H_{21}N_2O_2$, and the latter $C_{23}H_{26}N_2O_4 + 4H_2O$.

According to Flückiger, the seeds of nux vomica were introduced into Europe at the latest in the fifteenth century. At first they were only used to poison noxious animals. A Wittenbergian thesis, giving an account of toxicological experiments on dogs, dates from 1682 (J. Lossius, 'De Nuce Vomica'). This was followed by a few more writings of a similar character, but the oldest one with which I am acquainted, wherein nux vomica is mentioned as a medicine, was published in 1770.[1] It is still, however, doubtful

[1] J. B. Eberhard, 'Diss. de Nucis Vomicæ et Cortis Hippocastani virtute medica,' Halle, 1780.

whether this does not refer to the seeds of *Ignatia amara* or *Strychnos Ignatii*, St. Ignatius's beans, which contain as much as 1·5 per cent. strychnine. The isolation of strychnine from nux vomica by Pelletier in 1818, quickly made the old drug famous. A great number of experiments were then made with the new alkaloid. One of the earliest treatises upon it in Germany was a thesis for the Doctor's degree at Bonn,[1] in which seventeen experiments on animals are described. It is alleged in this that Magendie used strychnine with success in senile muscular weakness, and that Dieffenbach—the celebrated surgeon of later years, but then clinical assistant in Bonn—used it in paralysis.

We must first deal with the principal and most simple symptoms of strychnine poisoning.

I injected subcutaneously into a frog of medium size, about thirty minutes ago, a solution of $\frac{1}{40}$ mg. (0·000025 grm.) of strychnine nitrate in two drops of water. The animal sits apparently quite unaffected, but if you look more closely you will observe that the webs are somewhat stretched. If I now remove the glass shade, the animal does not jump away at once as is usually the case, but it seems to consider the point, so to speak, and then jumps, but obviously with difficulty. The respiratory movements are quicker and deeper than usual. If I lift the shade and then let it fall upon the glass plate, the animal shrinks just as if it were in great terror. If I repeat this five minutes later the animal is seized with general convulsions. The hind legs are extended, the webs are tensely stretched, the muscles of the thighs feel hard, the head of the animal is bent forward, the eyes are closed, and the fore-legs are crossed over each other[2]—the whole body resting upon these and upon the stretched toes like the arch of a bridge.

On making a closer examination we see that the contracted muscles are in a state of continuous movement. It is clear that the tetanus consists of a large number of single contractions following one another very rapidly. The clonic

[1] Th. Cramer, 'Strychnii vis ac efficacia in Corpus Animale,' 1820 (written in conjunction with Dieffenbach).

[2] This is only true of the males; the females extend their fore-legs.

stimulation of the muscles (κλονέω = to move strongly) has apparently become tonic (τείνω = to stretch).

If what the animal rests on, is not touched, then the muscles will relax, but any fresh irritation will cause tetanus. In the intervals between the spasms some slight respiratory movements may be noticed. The animal continues to have convulsive attacks and intervals of repose alternately for about twelve hours, and then slowly recovers.

All these symptoms are aggravated to such an extent when I give another injection of strychnine, that these intervals cease, and the single contractions of the muscles follow one another so rapidly that they are no longer visible.

If I were to repeat this experiment on warm-blooded animals you would have the same picture, but it would be more boldly drawn. The initial symptoms are quickly aggravated; all at once the legs of the animal, on some slight disturbance in the room, are violently contracted, and the animal itself is thrown several steps forwards. It falls upon its side with its head drawn WELL BACK, owing to the fact that the most powerful muscles of warm-blooded animals are the cervical and dorsal ones; at the same time all the extensors are strongly contracted. Respiration consequently stops at once (this, however, does not occur in the frog), the diaphragm remaining immoveable and in the position of deep inspiration during the whole attack. There is marked cyanosis of all the visible mucous membranes.

The same symptoms have been observed in human beings. As little as 0·03 gramme (½ of a grain) has proved fatal to an adult. It has been satisfactorily ascertained that the earliest symptoms of strychnine poisoning are formication, twitching, and rigidity of the limbs, whilst sensitiveness to light, to draughts and all noises has been noticed. The poison does not stimulate the brain to any marked extent, nor does it give rise to any feeling of dizziness.[1] Again, strychnine has practically no action upon the brain during the intervals between the spasms, and the intellect remains clear, except when asphyxia is threatened. A feeling of heaviness, pain, and extension in all the striated muscles precedes the con-

[1] E. Biernacki, "Ueber die Einwirkung des Strychnins auf das Grosshirn," 'Therap. Monatshefte,' 1890, s. 383.

vulsions; respiration, deglutition, and the power of speaking are rendered more difficult; great anxiety is shown by the most courageous patient. Isolated spasms occur, and any slight noise, or some gentle shaking of the bed or chair, will give rise to general convulsions, which are accompanied by cyanosis of the face, staring eyeballs, widely dilated pupils, swollen cervical veins, tightly closed mouth, and opisthotonos, so marked that the unfortunate patient is balanced on his occiput and heels—altogether a scene terrible to witness.

Where do the convulsions originate—in the cerebral or spinal centres, or in the periphery? This can be easily determined by dividing the motor nerves, as near as possible to their origin, shortly before poisoning an animal. The muscles supplied by these nerves do not then contract, although the poison circulates through them and through the endings of the nerves. On the other hand, if the blood-supply is cut off from a limb before the animal is poisoned, the muscular contractions will still take place.

The question as to what centres are specially acted upon by strychnine may be answered in the same way. If I decapitate this strychninized frog below the medulla oblongata, the spasms still continue. Of the three motor centres, brain, medulla oblongata, and spinal cord, the first two are now excluded; the last is consequently the one acted upon by the strychnine. This is also proved by the fact that in individuals suffering from paraplegia due to lesions in the upper part of the spinal cord, spasmodic contractions of the muscles of the legs can be caused by strychnine.

It might be supposed that strychnine causes the ends of the sensory nerves to become hypersensitive; consequently the effect of any peripheral irritation and its action on the spinal cord would be much augmented. But if we cut off the blood-supply of a limb by means of a ligature, and then poison the animal with strychnine, we cannot, on irritating the paws, detect any difference between the contractions[1] of this limb and the corresponding one of the other side.

With regard to the origin of the spasms, it is said that strychnine either paralyses the inhibitory centres of the

[1] G. L. Walton, 'Arch. f. Anat. u. Phys.,' 1882, s. 46.

spinal cord, or that it lessens the resistances that are normally present between the sensory and motor tracks and between the cells, so that the reflex action takes place more rapidly and is more pronounced, and any stimulus passing from the periphery to a single centre radiates thence to the other centres, and so affects the whole organism. There is nothing, however, to support such an explanation. Most authors consider that strychnine acts upon the LARGE GANGLION CELLS OF THE GREY MATTER of the anterior cornua.

The enormously increased activity of the reflex apparatus has been attributed by some authors to a direct stimulating action of the strychnine, and by others to an increase of excitability. It depends upon the dose which of these occurs. With small doses it is the latter ; the slightest perceptible external irritation is now sufficient to affect all motor nerves in the spinal cord. With large doses the former is brought about as well as the latter, so that the normal processes in the cells are sufficient to produce general convulsions.[1]

Death from strychnine in warm-blooded animals may be due to asphyxia produced by the frequently recurring or long-protracted spasms, which involve the respiratory muscles ; or it may result from exhaustion of the motor centres, a condition which is equivalent to paralysis of the protoplasm of the cells. We may conceive that the latter is due to the excessive activity of the protoplasm induced by the strychnine, or to the direct paralysis which follows the primary excessive excitement caused by this drug, and which, as we know, is the secondary effect of all other stimulants.

The observation that doses of strychnine, which prove fatal to a frog, do not injure invertebrate animals—crabs, leeches, snails, &c.—is of interest.[2]

Strychnine also increases the sensibility of the medulla oblongata and the vaso-motor centre, just as it increases the sensibility of the grey matter of the spinal cord. This is shown by the character of the respiration which we saw developed in the frog, and which also occurs in warm-blooded

[1] Freusberg, 'Arch. f. exper. Path. u. Pharm.,' 1875, Bd. iii, ss. 204 u. 348.

[2] W. Krukenberg, 'Vergleichende physiol. Studien,' 1880, Abt. 1, s. 95.

animals, as well as by the marked increase in the blood-pressure. This point has been investigated in animals. Curare was given to them, and the respiration then carried on artificially.[1] In this way the possibility of referring the increase of blood-pressure to general convulsions or to commencing asphyxia was excluded. In a similar experiment in which the spinal cord had been divided in the upper part of the cervical region, there was either no increase in the blood-pressure or at most a slight one. This proves that the increase is dependent, in the first instance, upon the vaso-motor centre, which is situated in the medulla oblongata.

The temperature of the blood is increased by strychnine[2] to a larger degree even than by caffeine, on account of the greater contraction of the muscles. This I showed as far back as 1872. In one case the temperature of a tetanised dog[3] rose to 44·8° C. (112·6° F.).

We have now to consider shortly the action of small non-poisonous doses of strychnine on HEALTHY INDIVIDUALS.

In the first place the drug has an extremely bitter taste, which is still perceptible in a solution of 1 to 60,000. Doses of two to three milligrammes ($\frac{1}{30}$ to $\frac{1}{20}$ of a grain) given twice or three times a day, increase the appetite and the quantity of saliva, as well as of the other digestive secretions. The digestion is improved. Vomiting seems to be induced solely by the nauseous taste of the alkaloids in the "nux vomica."

Careful investigations have revealed the action of strychnine on the sensory nerves.[4] One or two centigrammes ($\frac{1}{6}$—$\frac{1}{3}$ grain) taken internally increase the delicacy of the sense of smell within thirty minutes, and modify it in such a manner that any pleasant odour becomes still more agreeable, whilst an unpleasant one became much less so. This action on the olfactory nerve may continue for twenty-four hours, and even for several days, if 0·01 gramme ($\frac{1}{6}$ grain) mixed

[1] S. Mayer, 'Sitzungsber. d. Akad. d. Wissensch.,' Wien, 1871, Bd. lxiv, s. 663.

[2] Högyes, 'Arch. f. exper. Path. u. Pharm.,' 1881, Bd. xiv, s. 119.

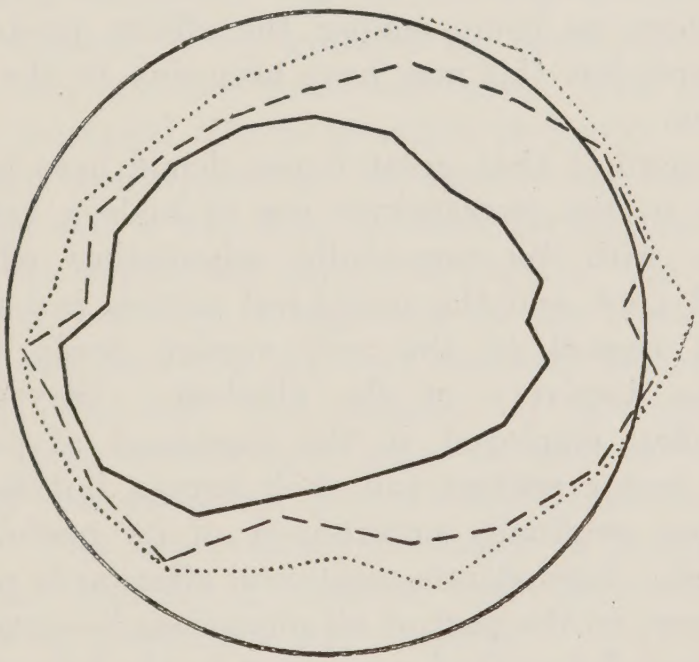
[3] Richet, 'Compt. Rend.,' 1880, vol. xci, pp. 131 et 443.

[4] Fröhlich und Lichtenfels, 'Sitzungsb. d. Akad. d. Wissensch.,' Wien, 1851, Bd. vi, ss. 329, 334, u. 345.

with a little sugar is applied directly to the mucous membrane of the nose for twenty minutes. Control experiments with either morphine or atropine gave opposite results. The peripheral sensibility of the cutaneous nerves is also increased by the action of strychnine.

The experiments which were performed by v. Hippel on himself,[1] and confirmed in their essential details by H. Dreser,[2] followed and were based upon the clinical results obtained by Nagel in 1871. The following changes are said to occur in healthy eyes. When 0·001 to 0·003 gramme ($\frac{1}{60}$ to $\frac{1}{20}$ of a grain) of strychnine is injected into the temporal region, the field of vision, especially for blue, is enlarged, acuteness of vision is transitorily accentuated, and the perception of a given point is increased at the

FIG. 27.



Blue on black ground.

——— Normal field of vision.

– – – – – – 15 minutes after injection of 0·003 gramme ($\frac{1}{20}$ grain) of strychnine.

. . . . . 24 hours later.

[1] v. Hippel, 'Ueber d. Wirkung d. Strychnins auf das normale u. kranke Auge,' Berlin, 1873.

[2] H. Dreser, 'Arch. f. exper. Path. u. Pharmak.,' 1894, Bd. xxxiii, s. 251.

periphery. This effect was produced within two hours; it seemed to reach its height in five hours, then persisted for three days, and finally disappeared three days later. No unpleasant symptoms were noticed after these injections. The reason why strychnine acts chiefly on the periphery of the retina may be that this part is normally less sensitive than the rest, and that if by any agent this sensitiveness is increased, the contrast at the periphery is rendered more striking. On the previous page is a diagram showing the results obtained by tracing the perimeters (simplified from v. Hippel's fig. 2, pl. i).

In one case a slight dizziness was experienced immediately after an injection of 0·004 gramme ($\frac{1}{15}$ grain) of strychnine nitrate, but it only lasted for three minutes. The elevated spirits, the increased action of the heart, and the greater sensitiveness to light which were reported by other authors as being among the effects produced, were not observed, but this may have been due to the smallness of the dose.

It was natural that great hopes should have been entertained as to the THERAPEUTIC USE of such a substance as strychnine with its powerfully stimulating effects upon the spinal cord and the peripheral nerves, just as was the case with regard to the nux vomica seeds themselves before the discovery of the alkaloid. Strychnine was naturally first employed in the treatment of paralysis of the great motor centres and their nerves, but the exaggerated hopes originally entertained of its usefulness were not fulfilled. Immoderate scepticism afterwards prevailed—not, however, on the part of all physicians [1]—until recently, when Naunyn [2] described, somewhat in the following terms, his fifteen years' experience of the remedy.

Permanent damage has not been observed to follow the

[1] Ziemssen u. Leube, 'Arch. f. klin. Med.,' 1869, Bd. vi, s. 266; L. Acker, 1874, Bd. xiii, s. 416; Kelp, 1874, Bd. xiv, s. 432; W. Reinhard, 'Deutsche med. Wochenschr.,' 1885, s. 326. See also Eulenburg, 'Hypodermat. Injectionen,' 1867, s. 243.

[2] Naunyn, 'Mittheil. a. d. med. Klinik zu Königsberg,' 1888. For ref. see 'Centralb. f. klin. Med.,' 1888, s. 879; 'Therap. Monatshefte,' 1889, s. 43.

use of strychnine. Its use is not attended with any success in complete paralysis, nor in paralysis which is by its nature progressive (tumours, multiple sclerosis); whilst beneficial results have been obtained when the morbid condition, whether subacute or chronic, *e. g.* diphtheritic paralysis and multiple neuritis, had become stationary. Favourable results were also frequently obtained in cases of incomplete paralysis such as paresis, in the paralysis following apoplexy, in chronic softening of the brain, in isolated sclerosis in the spinal cord, in poliomyelitis, and in incontinence of urine. The results were very satisfactory when the primary disease improved. It was observed that the pain in the paralysed portions of the body in chronic cases of hemiplegia, following an apoplectic seizure, was relieved by strychnine, though the paralysis itself was not at all improved.

The form employed for adults was a one per cent. aqueous solution, 0·005 gramme ($\frac{1}{12}$ grain) or less being injected daily into the paralysed limb. This amount was gradually increased to 0·01 gramme ($\frac{1}{6}$ grain). When the solution had been injected for ten days, its use was suspended for a week, and it was then injected for another ten days. Usually the injections were well borne, but sometimes they caused a feeling of tightness in the muscles, and in children, who as a rule are very sensitive to the action of strychnine, diarrhœa and spasms. If favourable results followed, these usually took place so soon as the dose in adults had been increased to 7 or 8 milligrammes ($\frac{1}{9}$ to $\frac{1}{8}$ of a grain). The improvement continued to be marked, and then became less so; it, however, again showed itself when the use of the strychnine was resumed.

v. Hippel came to the following conclusion, based upon the results obtained in ninety cases treated with strychnine:— "Strychnine acts upon the optic nerve in the same way as the constant current does upon other nerves. Its beneficial action was most successfully shown in cases which formerly were unaffected by our remedies, namely, in cases of atrophy of the optic nerve from the most varied causes."

Strychnine, when cautiously given, is certainly not nearly so dangerous as most physicians have regarded it; on the other hand, we are told that it is very liable to accumulate in

the system, and so to give rise to poisoning. Dragendorff,[1] after administering as large doses as possible for several days, did not find any strychnine in the urine of dogs for the first few days; he, however, found it there for several days after its administration had been discontinued, and also in the liver even when the animal had survived for some days after taking the dose. He also found it in the pons Varolii and medulla oblongata of both men and animals.

Cases of POISONING by strychnine are frequent in such countries as England and North America, &c., where the poison is more readily purchased than in Germany. In this country, however, cases occur quite often enough, but most of them are due to mistakes about medicines—mistakes either in dispensing, or from individuals taking medicines, containing strychnine, improperly or too frequently. Our chief aim in such cases must be to reduce the excitability of the spinal cord. Experience shows that this is best done by large doses of chloral hydrate, as this is antagonistic to the action of strychnine upon the ganglion cells and vaso-motor centres.[2]

If trismus makes it impossible to introduce the drug by the mouth, we can administer it by subcutaneous[3] or rectal injections. We must, however, not forget that subcutaneous injections of chloral hydrate are painful. A better plan is to introduce the drug by a soft catheter passed through the nose.

The patient must be kept absolutely at rest. The necessity for this can be shown experimentally. This frog, to which a medium dose of the poison has been given, and which rests under the bell-glass on a stand absolutely free from any vibration, shows no sign of spasm or convulsions, but only so long as it is left undisturbed. In the case of

[1] Dragendorff, 'Gerichtl. chem. Ermittelung von Giften,' 1876, s. 155; Kratter, 'Wien. med. Wochenschr.,' 1882, s. 214; E. Gay, 'Centralbl. f. d. med. Wissensch.,' 1867, s. 49.

[2] Husemann, 'Arch. f. exper. Path. u. Pharmakol.,' 1877, Bd. vi, s. 362.

[3] V. Faucon, 'Arch. génér. de Méd.,' 1883, pp. 74 et 153. Also C. W. Jones, 'Lancet,' 1889, vol. ii, p. 166; a man of thirty with marked tetanus, 1·25 gramme at first, and then 0·06 gramme subcutaneously; then 1·25 by the mouth, which could now be opened.

patients who have been poisoned by strychnine, such things as the opening of a door, the shaking of the bed, or the distant rumbling of a carriage will set up general convulsions.

The patient must drink large quantities of lukewarm water, in order that the poison may be removed from the circulation. If we think that there is still some poison in the stomach we must have recourse to tannin, for this substance forms a very insoluble compound with strychnine. A thick precipitate of tannate of strychnine is formed when I add a solution of tannin to a solution of nitrate of strychnine, and this becomes denser on the addition of dilute hydrochloric acid.

It has been shown in animals that energetic artificial respiration by means of bellows and an opening in the trachea can prevent asphyxiation by strychnine poisoning. Nevertheless we cannot avert death for more than a few hours, if doses sufficiently large to completely paralyse the spinal cord and heart have been given. The heart may beat for some time longer, and possibly the convulsions may become less violent. In the case of human beings, such artificial respiration as is above referred to is altogether impracticable on account of the violence of the spasms. I only refer to the matter here [1] in connection with the experimental investigations which have been made on animals.

I must also mention that the convulsions which are caused by strychnine may cease for as long a period as ten days, and that they often reappear when we think that the attacks have entirely ceased. In these latter cases the reflex organs, which are still over-sensitive, are gradually stimulated by the small quantities of poison which remain in the system, and then from some external irritation a sudden and unexpected explosion of energy takes place.

Brucine causes the same reflex convulsions as strychnine —a fact of which I have been repeatedly convinced. Its action when given in the same dose differs from that of strychnine only in small details ; it is not generally so

[1] Leube, 'Arch. f. Anat. u. Physiol., '1867, s. 629; Uspensky, ibid., 1868, s 523; Rossbach, 'Centralbl. f. d. med. Wissensch.,' 1873, s. 369; Brown-Séquard, 'Arch. de Physiologie,' 1872, p. 204; Buchheim, 'Arch. f. ges. Physiol.,' 1875, Bd. xi, s. 177.

marked, and does not last for so long a time.[1] Brucine is contained in the officinal Extractum Strychninæ, as well as strychnine, but is comparatively of little importance.

The preparations of AMMONIA AND ITS SALTS are closely allied to strychnine as far as their action on the central nervous system is concerned. The results are very similar, whatever acid is combined with the ammonium.

Violent clonic convulsions of the whole body are set up in a few minutes, if I introduce 10—30 centigrammes of a neutral soluble ammonium salt directly into the circulation of a warm-blooded animal. These convulsions differ from those caused by strychnine in the following points:—(1) The convulsive centres of the brain are affected, because all the motor nerves of the head are involved; (2) the cortex of the brain is insensitive before the convulsions occur, and at intervals when they are present; (3) the convulsions are not so markedly reflex in character, and occur without the intervention of any external stimulus.

If the dose is large enough in proportion to the weight of the body, the animal may die during one of the attacks, either from cessation of respiration owing to the spasms, or from rapid exhaustion of the respiratory centre.

A great number of experiments on animals, which in all essential points give the same results,[2] have been carried out since as far back as 1682. These were made with

[1] Ed. Liedtke, 'Die physiologische Wirkung des Brucins,' Königsberg, 1876, Doctordiss. unter v. Wittich's Leitung; Th. J. Mays, "The Physiological Action of Cocaine and of its Analogue, Brucine," 'Therapeutic Gazette,' 1885, June.

[2] Wibmer, 'Die Wirkung d. Arzneimittel u. Gifte im ges. tier. Körper,' 1831, Bd. i, ss. 119—146; C. H. Mitscherlich, 'Med. Zeitg. d. Ver. f. Heilk.,' 1841, Nos. 43—46; Böhm und Lange, 'Arch. f. exper. Physiol. u. Pharmak.,' 1874, Bd. ii, s. 364; Funke u. Deahna, 'Arch. d. ges. Physiol.,' 1874, Bd. ix, s. 416.

ammonium hydrate and with various salts of ammonia. Another series with a pathogenetic object was made with ammonium carbonate.[1] Any difference between the results of the latter experiments and of other investigators is due to the method which was employed being not only unsuitable but also confused. The ultimate result, however, is not affected. I may add in passing that, according to my former medical experiences, the spasms and drowsiness of uræmia in human beings, which occur in degeneration of the kidneys amongst other disorders, are very similar to those produced by artificial poisoning with ammonium salts. This has been contradicted, but the statement is nevertheless true.

We are not, of course, concerned here with the question as to the causation of these convulsions. I have merely referred to them as showing that the general action of the preparations of ammonium salts on the NERVES is one of STIMULATION. From our observations upon patients we are led to believe that they have a similar action upon the nervous centres and upon the heart.

The BLOOD-PRESSURE rises and the pulse becomes more frequent when ammonium salts are given to animals. This result is independent of the vaso-motor centre, for it also occurs when the spinal cord has been divided in the cervical region ; it is also independent of the convulsions, for it is brought about in animals under the influence of curare. Opinions still differ as to whether the rise in the blood-pressure is caused by a stimulation of the heart alone or by a simultaneous stimulation of the vaso-motor apparatus. I have repeated these experiments,[2] and I have succeeded in producing a rise of blood-pressure without using curare or artificial respiration, and without causing any convulsions ; for instance, in the case of a rabbit weighing 1850 grammes the blood-pressure rose from 112—126 after the injection of

[1] Frerichs, 'Die Bright'sche Nierenkrankheit und deren Behandlung,' 1851, s. 281 ; Oppler, 'Arch. f. path. Anat.,' 1861, Bd. xxi, s. 260; Petroff, ibid., 1862, Bd. xxv, s. 91 ; Rosenstein, ibid., 1872, Bd. lvi, s. 383.

[2] A. van der Helm, 'Versuche über einige arzneiliche Erregungsmittel,' Doctordiss, Bonn, 1887 ; 'Centralbl. f. klin. Med.,' 1888, s. 25.

0·3 gramme of ammonia chloride. In order to exclude the possibility of irritating the skin, smaller doses were injected into a prepared vein, every possible source of external stimulation being avoided. Exactly the same results were obtained in this way.

Respiration is affected in the same manner. This point was investigated with doses of ammonium chloride which were not sufficient to cause convulsions, according to the method which, as you may still remember, was used in experimenting with morphia. In this manner it was shown that the injection of 0·05 gramme of ammonium chloride and a little water into the jugular vein of a healthy rabbit weighing 2200 grammes, increased the respirations by one fifth. This effect soon passes off, but is again produced by another injection of the same dose, and, in fact, takes place even after a third injection. If the dose is doubled the same result is obtained, with the exception that it brings on a slight attack of convulsions. To another animal, weighing 1400 grammes, in which the number of respirations had been reduced from 390 to 150 by chloral hydrate, a subcutaneous injection of 0·1 gramme (1½ grains) of ammonium chloride was given. The respirations were increased to 300, but only for a short time, and we found that a repetition of the dose did not prevent a further fall.

The effect of ammonium chloride in all my experiments was very transitory. This seems also to be the case in human beings, and may be the reason why ammonium salts are no longer regarded as general stimulants.

I show you the preparations which are officinal with us.

1. Liquor Ammonii Caustici, liquid ammonia, caustic ammonia, is a solution of the vapour of ammonia, NH_3, in water, and is a clear, colourless, volatile liquid, with a pungent odour and strongly alkaline reaction. It forms a dense white cloud with the vapour of hydrochloric acid, and contains 10 per cent. of ammonia. Its specific gravity is 0·960. The gas was formerly prepared by treating ammonium chloride, NH_4Cl, with a strong caustic alkali, so that water, the corresponding chloride, and ammonia are formed according to the equation $NH_4Cl + KOH = H_2O + KCl + NH_3$. Hence its former name, spirit of ammonia. It is now usually prepared

from the ammonium sulphate obtained in the purification of coal gas.

The strongly irritating action of the vapour of this preparation makes it useful in cases of fainting. Care, however, must be taken that the patient does not inhale too much of it, as cases[1] have occurred in which the poison irritated the respiratory passages, and caused death from the resulting inflammation. The following case occurred lately in Bonn. A child fifteen months old inhaled the vapour from a very dilute solution of ammonia for some time. The pharynx became congested, and stupor with persistent vomiting intervened. The last symptom may be rightly considered as due to the fact that the brain was affected.

Solution of caustic ammonia is employed for various purposes, and is a constituent of the following preparation.

Liquor Ammonii Anisatus, which contains one part of oil of aniseed, twenty-four parts of alcohol, and five parts of solution of ammonium, is a clear yellowish liquid, with the odour of oil of aniseed.

Ammonia, on account of its alkaline reaction and its stimulating effect upon the skin, is contained in three of the liniments of the German Pharmacopœia. The relative importance of the effects produced by the several components, by the free alkali, by the rubefaction of the skin, and by the massage of the affected parts when using these liniments, has not yet been investigated.

The liniments are—Linimentum Ammoniatum, a volatile liniment. This is a white, viscid, homogeneous mixture of three parts of olive oil, one part of Liquor Ammonii Caustici, and one part of Ol. Papaveris.[2]

Linimentum Ammoniata Camphoratum, volatile camphor liniment. Three parts of Ol. Camphoratum with one part of Liquor Ammonii Caustici and one part of Oleum Papaveris.

Linimentum Saponata Camphoratum[3] contains ammonia, soap, camphor, alcohol, and the oils of rosemary and thyme.

[1] See Eulenburg, 'Schädl. u. gift. Gase.,' 1865, s. 194.

[2] In the Linimentum Ammoniæ of the Ph. Brit. the Ol. Papaveris is omitted.—*Transl.*

[3] Also called Opodeldok, a curious name derived from ὀπός = juice, δήλησις = injury, δοχός = fixing.

It is nearly colourless, slightly opalescent, and semi-solid, though it is readily liquefied by the heat of the hand.

2. Ammonium Carbonicum, ammonium carbonate, consists of thin, hard, translucent, crystalline masses, with a strong ammoniacal odour, which effloresce on exposure to the air with the formation of a white powder on the surface. The salt volatilises when heated, and dissolves slowly but completely in five parts of water. Owing to the first of these properties it was formerly called *sal volatile*. It was also, in alchemistic times, called *sal cornu cervi*, because it could be obtained by heating various kinds of animal matter, including hart's horn. Its composition varies on account of the great volatility of ammonia. When neutral its formula is $(NH_4)_2CO_3 + H_2O$. Formerly it was considered to be a sesquicarbonate, on account of the evaporation of the ammonia. It was afterwards shown[1] that the composition of the officinal salt was more complicated, and varied according to the duration of its exposure to the air. It finally becomes an acid salt with the formula $NH_4O.OH.(CO_2)_2$. The white powder mentioned above as being formed on the surface of ammonium carbonate, is $NH_4.HCO_3$. When used medicinally, we must remember that it exerts a caustic action upon mucous membranes. It was formerly classed as a cardiac and nervous stimulant.

3. Ammonium Chloratum, Ammonium chloride, sal-ammoniac, ammonium muriaticum (from *muria* = brine), consists of hard, white, fibrous, crystalline masses; it also occurs as a white, colourless, crystalline powder which does not decompose in the air, has a disagreeable salt taste, volatilises on heating, and is soluble in three parts of cold or hot water, but very insoluble in alcohol. The salt is given chiefly, when the respiratory passages are swollen or inflamed, to render tenacious mucus less viscid, and to promote expectoration. Its action has not been thoroughly investigated. It may be either taken in solution or inhaled; in the latter case it is gently heated in a saucer over a spirit flame in a warm room, and so volatilised. Some patients can breathe more comfortably in an atmosphere which is laden with it.

Ammonium chloride is in this case decomposed into NH_3

[1] H. Vogler, 'Zeitschr. f. Analyt. Chemie,' 1878, Bd. xix, s. 451.

and HCl, as may be easily shown by holding a long glass tube of about 2 cm. diameter over the heated salt. The vapour from the ammonium chloride in the saucer turns red litmus paper blue, whilst the vapour in the upper part of the glass tube reddens blue litmus paper. The two substances again reunite in the air to form the neutral salt.

4. Liquor Ammonii Acetici, solution of ammonium acetate. This is prepared by mixing five parts of the ammonia of the German Pharmacopœia with six parts of dilute acetic acid at the boiling-point, neutralising the liquid with ammonia, and diluting it with water until it has a specific gravity of 1·033. It is a clear, colourless, neutral or slightly acid fluid, which is entirely dissipated by heat, and which contains 15 per cent. of ammonium acetate, $NH_4.C_2H_3O_2$. The salt, on account of its deliquescent character, is not officinal.

This preparation, under the name Spiritus Mindereri, was formerly much employed as a sudorific, either alone, in doses of a teaspoonful, or in conjunction with other substances. In more recent times we lost faith in any action of this kind, until Marmé [1] experimented with it on cats, after he had become acquainted with the sudorific effect produced by a few milligrammes of pilocarpine. A subcutaneous injection of the preparation caused sweating in all the animal's paws. Ammonium acetate, like all salts of acetic or other vegetable acids, combines with oxygen in the body, and is converted into a carbonate.

We may add the statement, although it has little or no importance therapeutically, that the ammonium salts of carbonic acid or of the vegetable acids are to a large extent changed into urea in warm-blooded animals, and can be isolated as such in the urine. Ammonium chloride is also largely converted into urea in herbivorous animals, whilst in carnivorous animals at least half of what has been taken undergoes this change.[2] In the human organism it disappears to a very large extent, but probably reappears as urea in the urine.

[1] Marmé, 'Nachr. d. königl. Ges. d. Wissensch. in Göttingen,' 1878, No. 3.

[2] See E. Salkowski, 'Zeitschr. f. phys. Chem.,' 1877, Bd. i, s. 1; J. Munk, ibid., 1878, Bd. ii, s. 29; Adamkiewicz, 'Arch. f. Path. u. Anat.,' 1879, Bd. lxxvi, s. 377.

XV.

History of ethyl alcohol—Glucose and yeast—Stimulating action—Its effect on the temperature of healthy individuals—On nutrition—Stimulant for healthy people—Is alcohol oxidised in the organism?—Decomposition of albumen—The use of alcohol—Cause of the fall of temperature—The different beverages—Wine as a remedy—Experiments on digestion—Alcoholism—Poisonous properties of the collateral products in the distillation of ethyl alcohol.

ALCOHOL, or ETHYL ALCOHOL, occupies an important place in therapeutics. Its effects are varied, but it is used, like the remedies discussed in the last lecture, mostly as a stimulant and restorative.

Alcohol was first known as a product of the distillation of wine. This process is believed to have been in use as early as the eighth century; at any rate, it is described by Marcus Græcus, who is supposed to have lived at that time. Geber, an Arabian alchemist who lived at Sevilla about the same time, uses the term AQUA VITÆ for alcohol. Arnold of Villanova, and Raymond Lully (1315) were the next to devote attention to it; but it was not until the year 1400 that the German Benedictine Monk, Basil Valentine, obtained it almost free from water; he re-distilled the product several times with calcined cream of tartar, that is to say potassium carbonate, until after igniting it in a glazed dish, "keine aquositas in funda bleibet."[1] In 1796 the two German chemists, Lowitsch and Richter, both succeeded, independently of each other, in preparing absolutely anhydrous alcohol. Lavoisier discovered that the substance consisted of carbon, hydrogen, and oxygen, and De Saussure in 1814 determined its percentage composition. Th. Schwann, in Berlin, and Cagniard-Latour, in France, discovered in 1836, independently

[1] No moisture was left.

of each other, the yeast fungus, and held that it was the cause of alcoholic fermentation. The name alcohol is of Arabian etymology. Very finely powdered black sulphide of antimony, which is used by women in the East to colour their eyebrows, has been known for centuries by the name of "Kohol." Alchemists called finely pulverised gold, alcohol auri, and, in German pharmacy, pulvis alcoholisatus still means a very fine powder. The same meaning was attached to alcohol vini—a liquid distilled from wine and separated from water—which spontaneously evaporates and dissipates itself in the most minute form. The name "Weingeist" (spirit of wine) seems to have originated with Basil Valentine.

At first no one thought of using alcohol as a general beverage. It was sold by druggists as a secret remedy which was to prolong life, restore youth, and bring about other desirable results. It was consequently also called Aqua juventutis. "Mankind has grown old," said Arnold of Villanova,[1] "and has become feeble; therefore God has given him this water of life, that he may grow young again. It will be the source of a new life for mankind." Michael Savonarola—who died in 1462, a famous physician in Padua, and grandfather of the unfortunate monk of the same name—relates that a famous contemporary on reaching his eightieth birthday exclaimed, "O aqua vitæ, per te jam mihi vita annis viginti duobus prorogata fuit!" When such views were held regarding the action of alcohol, it was no great step to discover that it possesses qualities which render it valuable in therapeutics; this is shown by the title of Savonarola's work[2]—"De arte conficiendi Aquam vitæ, deque ejus vi admirabili ad conservandam sanitatem et corporis humani ægritudines curandas." These properties of alcohol have also been demonstrated from that time up to the present in an uninterrupted series of medical writings, treating of aqua vitæ.

Spirit of wine, or ethyl alcohol, or simply alcohol, is the

[1] See the edition of his works published at Leyden, 1504, pp. 86 and 89.

[2] H. Beigel, "Ein Gedicht von 1559 über den Branntwein," 'Arch. f. pathol. Anat.,' 1864, Bd. xxx, s. 246.

result of the fermentation of grape sugar and fruit sugar, which takes place in the presence of the yeast fungus. The whole process may be represented by the formula, $C_6H_{12}O_6 = 2CO_2 + 2C_2H_5.OH$; but it is not quite so simple. Small quantities of other substances containing oxygen, are formed, among which glycerine and succinic acid are most prominent, together with homologous alcohols, ranging from propyl to octyl, and also aldehydes. About 6 per cent. of the sugar employed is lost in the formation of these collateral products.

The yeast fungus,[1] *Cryptococcus vini* or *cerevisiæ*, belongs to the family of Protomycetes, which are fungi of the simplest kind. When present in large quantities it forms the slimy, usually brownish mass, which has been noticed for a long time at the bottom of liquids after they have undergone fermentation. It has been called yeast. When examined microscopically it is seen to consist of innumerable oval cells. These increase, by sprouting, in the nutritive fluid, and form chains and groups, with cells branching out from them. The yeast fungus decomposes grape-sugar or glucose, and fruit-sugar or levulose, by a vital process, and not by means of an amorphous ferment extracted from it.

Alcohol can also be synthetically prepared from its elements. If we ignite the ends of two pieces of charcoal by an electric current, in hydrogen gas, we obtain the gas acetylene, C_2H_2, which, when treated with nascent hydrogen in a solution of ammonia, yields ethylene or olefiant gas, C_2H_4; on agitating this with sulphuric acid, it is dissolved, and forms ethylsulphuric acid, $C_2H_6SO_4$. This latter body, on being heated with water, is decomposed into sulphuric acid and alcohol ($C_2H_6SO_4 + H_2O = H_2SO_4 + C_2H_5.OH$).

Chemically pure alcohol is volatile, and boils at 78° C. It can therefore be separated, to a great extent, from its watery solutions by distillation; this proceeding, however, is not sufficient, if we wish to obtain the alcohol in an anhydrous condition, as it has a great affinity for water, and carries some

[1] Th. Schwann, "Vorläufige Mitteilung betreffend Versuche über die Weingärung und Fäulnis," 'Ann. d. Physik und Chemie,' 1837, Bd. xxxi, s. 184; Cagniard-Latour, "Mém. sur la Fermentation vineuse," 'Ann. Chim. physique,' 1838, vol. lxviii, p. 206.

over in its vapour. It is entirely deprived of water by means of anhydrous salts, such as copper sulphate, or by metallic sodium. Its specific weight is 0·7939 at 15° C. (59° F.).

The ACTION OF ALCOHOL differs according to the way in which, and the part to which, it is applied, and also according to the quantity employed. With regard to its external use, we find, in the first place, that it checks PUTREFACTION AND FERMENTATION, properties which are of importance in therapeutics. Alcohol exhibits the latter reaction even in the process by which it is obtained. If the quantity of sugar in the "must," or juice of the grape, is too large, the action of the yeast cells, after a certain time, becomes distinctly slower; and, when the "must" contains about 17 per cent. of alcohol, the remaining sugar is not decomposed, because the action of the yeast cells is now paralysed or stopped by the alcohol. The explanation of its antiseptic action is similar. Alcohol, if not too much diluted, prevents the formation of putrefactive bacteria, and if they are present and fully developed, puts a stop to their action. It does not act as an antiseptic by extracting water; urine, for instance, the putrefaction of which can be prevented by the addition of 20 per cent. of alcohol, contains enough water for its decomposition, and would, without the alcohol, still undergo putrefaction, even if we evaporated away 20 per cent. of the water. Of course, if all the water has been withdrawn from any tissue by means of alcohol, putrefaction can no more take place in it than would be the case if this tissue had been dried up by exposure to a hot sun. Alcohol, however, seldom extracts all the water from a tissue.

Alcohol produces a local STIMULATING effect upon the tissues; and this is also to a certain extent the case when it is given internally.

I will briefly enumerate the results of some experiments—in cases free from disease—which were made for the purpose of inquiring into the stimulating action of alcohol.

Cl. Bernard noticed that concentrated alcohol caused, in dogs, a considerable decrease of the gastric and pancreatic secretions; this was not, however, the case when the alcohol

was freely diluted with water, for the secretions were then increased.[1]

Parkes and Wollowicz made experiments on a healthy man of twenty-eight who usually drank ½ to 1 litre (17½ to 35 oz.) of beer every day. For ten days he drank no beer, and then he was given at intervals from 28 to 220 c.c. (1 to about 7½ oz.) of rectified spirit a day, and on some days 340 c.c. (about 12 oz.) of good cognac containing 48 per cent. of absolute alcohol. The PULSE during the ten days of abstinence averaged 73·5 a minute; during the period when the man took the rectified spirit, it was 88·5; and when the brandy was taken, 91·4. When the administration of alcohol was discontinued, some days elapsed before the pulse fell to its former rate. The investigators drew the following conclusions from 150 pulse curves, some of which appear in the paper.[2] Alcohol causes a more rapid and stronger contraction of the left ventricle, which therefore works harder in a given time, and has shorter intervals of rest. The blood circulates through the capillaries more freely than usual. Parkes afterwards repeated these experiments on healthy men, using good claret and brandy; the results obtained were essentially the same.

Experiments made on dogs gave similar results.[3] If the dose of alcohol was small, and some time elapsed before it reached the heart, the ARTERIAL PRESSURE was increased; if, on the other hand, the dose was large, the pressure was lowered.

We are apparently justified in ascribing the increased rate of the pulse in the human subject solely to the dilatation of the arteries and capillaries, for we know that the heart beats more frequently as soon as the arteries are dilated. This is a compensatory arrangement for the purpose of keeping up the blood-pressure, which, when the amount of the blood remains constant, depends upon the character of the contractions of the heart, the number of its contractions, and the

[1] Cl. Bernard, 'Les effets des substances tox. et méd.,' Paris, 1857, pp. 430 et 433.

[2] E. Parkes, "Experiments on the Effects, &c., of Alcohol," 'Proceedings of the Royal Soc.,' 1870, Nos. 120 and 123; 1875, No. 150.

[3] Albertoni e Lussana, 'Lo Sperimentale,' 1874, vol. xxxiv.

calibre of the arteries. The number of contractions is increased as soon as the vessels begin to dilate. But this consideration does not prevent the possibility of our making use of the above facts in DISEASES in which only the freer and fuller circulation of the blood in the vital organs can act as a stimulus. And, moreover, experiments which I made in the year 1869 have shown, that the increased activity of the heart may not depend solely upon the dilatation of the arteries. The number of heart-beats increased to the same extent, when alcohol was introduced into the stomachs [1] of large dogs in which extreme dilatation of the arteries had been obtained by cutting off the connection between the vascular nerves and the chief vaso-motor centre.

As regards RESPIRATION, the most important and vital function next to the action of the heart, no definite results have been obtained hitherto in any of these experiments. This is owing to the imperfect methods employed. Zuntz found that, in healthy human beings, small doses of alcohol increased the respiration, that is the quantity of air inhaled and exhaled, on an average, by 9 per cent. ; whilst J. Geppert, in a work to which we shall refer later on, arrived at the following figures with regard to the action of non-intoxicating doses of alcohol :

The volume of air respired during ten minutes (estimated in litres).

Original quantity.	After alcohol.	After ten minutes.	Percentage increase in the second column.
57	62	59	+ 8·7
61	57	55	— 6·7 [2]
55	60	56	+ 9·0
54	57·5	52	+ 6·5
55	60	57	+ 9·0
45	49	—	+ 9·0
53	56	51	+ 6·0
54	59	53	+ 9·0
51	59	57	+ 15·0

[1] C. Binz, "Ueber die antipyretische Wirkung von Chinin und Alkohol," 'Arch. f. path. Anat.,' 1870, Bd. li, s. 153.

[2] This number is the only one in all our experiments which showed a

The mean of these experiments shows an increase of a little over 7 per cent. The increase of 15 per cent. in the last experiment also continued for the longest time; it was due to the action of a good German sparkling wine.

In warm-blooded animals I succeeded, by employing the same method, in increasing the respiratory volume 90 per cent. The increase lasted one hour.[1] This was also the case when I injected diluted alcohol directly, and without the least external irritation, into a vein. Thus the objection that the stimulating action of alcohol is only due to the local irritation of the part at which it is introduced, falls to the ground.

I have already alluded to the action of alcohol upon DIGESTION. This question deserves special consideration, since it has been argued, from the results of certain experiments upon digestion, which were carried out on human beings as well as in the laboratory, that alcohol has an injurious action upon the normal assimilation in the intestines. I will give you an account of the latest experiments, which are of great value because they avoid the mistakes formerly made, and are corroborated by our everyday experience.

One hundred c.c. of olive oil were introduced into the stomachs of adults, which had been previously washed out with tepid water; two hours afterwards all the contents which had not passed into the small intestine, were removed by the stomach-pump. The activity of the stomach was increased in six experiments by the action of moderate doses of alcohol, that is to say, less oil was removed from the stomach. The decrease in the quantity of oil removed in the fourth experiment amounted to 52 per cent.[2] Eight small teaspoonfuls of brandy were given during the hour succeeding the introduction of the oil.

decrease in the volume of respiration under the influence of alcohol. It was probably due to some mistake—which cannot now be traced—in the experiment, or in noting down the figures.

[1] N. Zuntz und Berdez, 'Fortschritte der Med.,' 1887, s. 1; J. Geppert, 'Die Einwirkung des Alkohols auf den Gaswechsel des Menschen," 'Arch. f. exper. Path. u. Pharmak.,' 1887, Bd. xxii, s. 368; C. Binz, 'Centralbl. f. klin. Med.,' 1891, s. 1.

[2] G. Klemperer, "Alkohol und Kreosot als Stomachica," 'Zeitschr. f. klin. Med.,' 1890, Bd. xvii, s. 324 (Supplement-Heft).

In adults, 30 to 40 grms. of brandy, containing 50 per cent. of alcohol, ACCELERATED the gastric digestion by about thirty minutes, when taken either in single or divided doses. Red as well as white wine PROMOTED digestion, when taken either before or during a meal. Large doses of brandy had an opposite effect.[1] Large quantities of light beer maintained the nutrition of individuals who lived upon an insufficient vegetable diet.[2]

Small quantities of alcohol accelerated the absorption, in warm-blooded animals, of substances such as potassium iodide, which were given through a Thiry-Vella fistula in the intestines. When patients took potassium iodide in water or milk, to which a moderate amount of alcohol was added, a larger quantity of iodine was, as a rule, observed in the urine within a given time, than when no alcohol was given.[3]

The experiments in which alcohol appeared to have an unfavourable effect, referred always, as far as I know, to the digestion in the stomach. It has since been shown, however, that the chief part in the process of digestion [4] certainly does not take place in the stomach. If, therefore, some slight decrease in the peptonisation of albumen is brought about by the administration or addition of alcohol, this is of no consequence in comparison with the chief work of the intestinal canal, which takes place in the small intestines.

The KIDNEYS also are stimulated to greater activity by moderate doses of alcohol. This was shown by the effect of beer, and still more by that of wine, on the quantity of urine secreted.[5] The quantity of urine in five hours was increased to 385 c.c. by 1 litre (35 oz.) of water; to 629 c.c. by 1 litre of Seltzer water; to 1012 c.c. by 1 litre of Munich beer; and

[1] Penzoldt und R. Wolffhardt, 'Münch. med. Wochenschr.,' 1890, s. 608.

[2] Zuntz und Magnus Levy, 'Arch. f. d. ges. Physiol.,' 1891, Bd. xlix, s. 438.

[3] Leubuscher, 'Verhandl. des. 9 Congr. f. innere Med. in Wien,' 1890, s. 436; See also Rumpf, 'Deutsche med. Wochenschr.,' 1889, No. 43.

[4] See among others C. V. Noorden, "Ueber die Ausnutzung der Nahrung bei Magenkranken," 'Zeitschr. f. klin. Med.,' 1890, Bd. xvii, s. 137.

[5] R. Mori, 'Arch. f. Hygiene,' 1888, Bd. vii, s. 354, Münch. Hyg. Inst.

to 1600 c.c. by 1 litre of wine. The administration of a decoction of hops, 4 parts in 1000, caused irritability of the bladder,[1] but no great diuresis. The action of alcohol only becomes marked when a large quantity of water has been simultaneously given, so that the blood is well charged with it; $\frac{1}{10}$ of a litre of a 40 per cent. solution of alcohol only caused the secretion of 533 c.c. of urine, whilst 1 litre of a 4 per cent. solution raised it to 961 c.c.

The stimulating effects which small doses of alcohol produce in different parts of the body may, here and there, possibly be due to paralysis of the inhibitory apparatus. This is a point, however, about which we know nothing.

Many experiments have been made with regard to the effect of alcohol on the TEMPERATURE of the body. The first observations on this, as far as I know, were made incidentally to another investigation in 1845.[2] They were followed by other investigations,[3] but neither these nor subsequent ones have had any influence whatever on scientific views or medical practice. Every one was under the general impression that the heat of the human organism was sensibly INCREASED by alcohol. The experiments which have been made here under my supervision since 1868, and which I partly carried out myself,[4] removed this mistaken idea, and quickly led the way to the administration of alcohol to patients after a method which is in conformity with its action. I was not aware of the experiments previously mentioned; my starting-point was the following consideration:

[1] Nutmeg administered at the same time prevented this.

[2] H. Nasse, 'Med. Correspondenzblatt für rheinische Aerzte,' 1845, s. 346.

[3] Duméril et Demarquay, 'Archives génér. d. méd.,' 1848, vol. xvi, p. 334; Lichtenfels und Fröhlich, 'Denkschriften der. k. k. Akademie zu Wien,' 1852, s. 131.

[4] C. Binz, 'Sitzungsber. Niederrhein. Ges. f. N. und Heilk.,' 1869, 7 Juni; 'Berl. klin. Wochenschr.,' 1869, s. 334; C. Bouvier, 'Arch. f. ges. Physiol.,' 1869, Bd. ii, s. 370, und 'Doctordissert.,' Bonn, 1872 (published by A. Hirschwald, Berlin); M. Mainzer, 'Doctordissert.,' Bonn, 1870. Ref. 'Arch. f. pathol. Anat.,' 1870, Bd. liii, s. 529; P. Daub, 'Doctordissert.,' Bonn, 1874, und 'Arch. f. exper. Path. u. Pharmak.,' 1875, Bd. iii, s. 260; G. Strassburg, 'Arch. f. pathol. Anat.,' 1874, Bd. lx, s. 471; G. Bodländer, 'Zeitschr. f. klin. Med.,' 1888, Bd. xiii, s. 401.

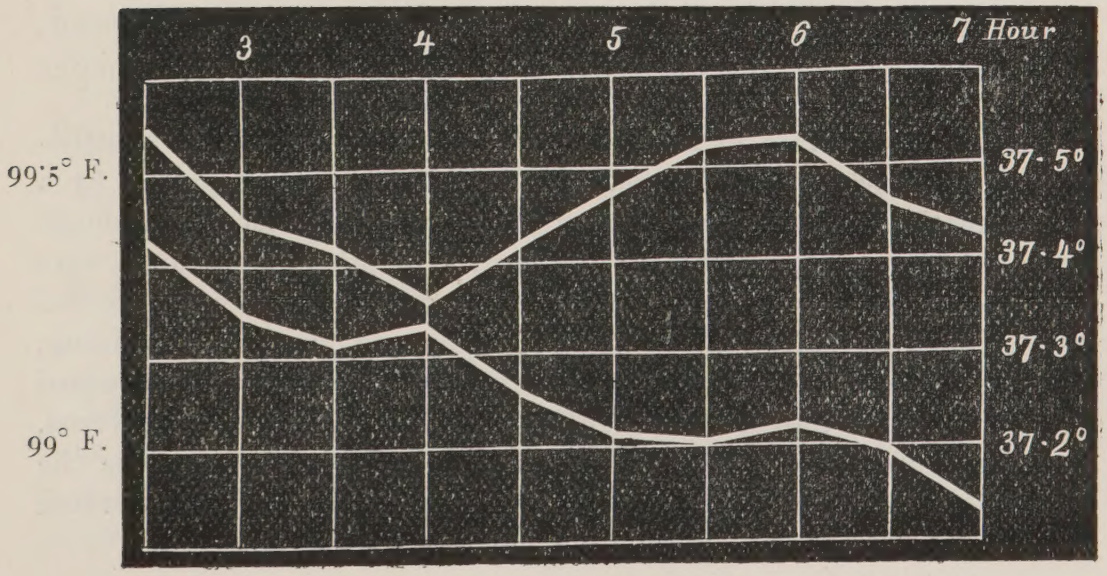
When physicians give alcohol freely, in large doses, as a stimulant in high fever, we often see some improvement in the condition of the patient. This could not be the case if the general view, that it increases the temperature, were the right one; consequently a febrile temperature, at all events, cannot be increased by alcohol.

The scope of this supposition was confirmed and widened by a series of experiments upon animals in which I produced high fever by injecting septic matter. The present state of our knowledge of the action of alcohol upon the normal temperature is as follows:

In healthy adults the thermometer shows no rise of temperature in the rectum after *small* quantities have been taken, although a feeling of increased warmth is experienced in the stomach, and afterwards in the skin. MODERATE quantities of about 30—80 grms. (from 1 to 3 oz.), which need not be sufficient to cause intoxication, cause a fall of 0·3° to 0·6° C. (0·5° to 1° F.); this even occurs when the temperature at the time of the experiment is rising towards its daily maximum. The lowering of the temperature is very trifling when such quantities are taken by people accustomed to the use of alcohol. When given in NARCOTIC DOSES alcohol lowers the temperature several degrees and for several hours.

I have here one of Daub's charts, which shows clearly the effect of moderate doses. It gives the result of 126 observa-

FIG. 28.



tions on a healthy man, eighteen years old, who was treated in the orthopædic department of the surgical clinic at Bonn, but who was in good health and free from fever. A single dose of 30 to 50 c.c. (8 to 14 drachms) of rectified spirit containing 98 per cent. of absolute alcohol diluted with a little water, and mixed with some sugar, was given in the afternoon. The upper line shows the temperature in the afternoon when no alcohol was given, the lower line represents the temperature in the afternoon when alcohol was given.

The erroneous idea that the blood becomes WARMER when alcohol is taken, depends upon the fact that the blood-vessels in the stomach and also in the skin dilate. An increased sensation of warmth is consequently felt by the nerves of both stomach and skin, and, as we are accustomed to estimate the temperature of the entire body from the temperature of the skin, it was necessarily thought that alcohol raised the temperature, until this was disproved in more recent times by means of the thermometer.

I shall have to discuss later the reason why alcohol, when it affects the temperature of the body, always depresses it.

The effect which alcohol has upon the NUTRITION of sick people is of the greatest importance. Of course we can only consider the so-called respiratory and not the recuperative changes.

As long as the experiments made at Paris[1] in the year 1860, according to which alcohol is eliminated from the system "en totalité et en nature," were considered authoritative, there could be no doubt that it has no nutritive value whatever. This view was so completely accepted, that neither the previous German experiments at Dorpat

[1] Lallemand, Perrin, et Duroy Duc, 'Rôle de l'alcohol et des anesthésiques dans l'organisme,' Paris, 1860. These observers proved by a very sensitive reagent—a solution of potassium bichromate in sulphuric acid—that traces of alcohol, and of course of other substances, were excreted by the skin and lungs; they proved the excretion of alcohol by the kidneys, partly in the same manner, and partly by obtaining, from the distillation of urine, an inflammable liquid which contained alcohol. But as they did not mention the amount of alcohol recovered, nor could any of the numerous believers in this theory state the amount, their conclusion that all the alcohol taken was excreted unchanged is, to say the least, unproved.

which gave different results, nor a subsequent English refutation,[1] nor the more recent investigations of my pupils, were able to displace it. An exact and authoritative investigation of this subject was therefore necessary.

An investigation of this kind was carried out in my laboratory [2] in 1883, which, besides showing the sources of error of the French investigators, clearly demonstrated the following facts:

When moderate doses of alcohol were taken, the greater part of it was excreted by the kidneys and the lungs, a very small quantity by the skin, but none by the bowels. Altogether about 3 per cent. of it was recovered from healthy adults; in dogs 0·6 per cent. more was obtained. Thus:

Excretory organ.	In dogs.		In men.	
	Number of experiments.	Percentage quantity excreted.	Number of experiments.	Percentage quantity excreted.
Kidney . . .	4	1·576	12	1·177
Skin	2	—	3	0·140
Lungs	3	1·946	3	1·598
Bowels	—	—	1	0·0
Total . . .		3·522		2·915

The quantity arrived at, as being excreted through the kidneys in man, agrees very well with the average of twenty-two experiments which were made some time ago in my laboratory, viz. 1·115.[3] These were carried out with a vaporimeter which showed the presence of as small a quantity as 0·05 per cent. To investigate the excretion of the alcohol by the skin and lungs, a HEALTHY man was put in a tepid bath,

[1] Anstie, 'Stimulants and Narcotics,' London, 1864, p. 419.

[2] G. Bodländer, "Die Ausscheidung aufgenomenen Weingeister aus dem Körper," 'Arch. f. d. ges. Physiol.,' 1883, Bd. xxxii, s. 398.

[3] H. Heubach, 'Arch. f. exper. Path. u. Pharmak.,' 1877, Bd. vi, s. 287, und 1878, Bd. viii, s. 446.

and then, after an interval, was enclosed for four hours in an air-tight cylinder, which was well ventilated by an aspirator —sometimes with his head projecting, sometimes without. The air after passing through the cylinder was drawn through sulphuric acid and potassium bichromate in a sufficiently large number of bottles to ensure that the solution in the last was no longer discoloured. The quantity of alcohol, which passed through, could in this manner be easily shown colorimetrically. Any doubt in the colorimetrical estimation was given in favour of the excretion.

Strassman, of Berlin, repeated our experiments, using another method, and came to the conclusion that about 4 per cent. of alcohol was excreted.[1]

Heubach and I have shown that the quantity of alcohol excreted by the kidneys IN FEBRILE PATIENTS is similarly very small, or sometimes even *nil*.

Aldehyde or acetic acid was not found in the urine; it is therefore probable that the alcohol, except the small amount recovered by my assistants and myself as above stated, is oxidised in the tissues to carbonic acid and water, with the intermediate formation of aldehyde and acetic acid. By this combustion of alcohol, heat is produced, which supplies the vital energy necessary to life. If we make a simple arithmetical calculation of its colorimetrical value, we find that the nutritive value of 1 litre of average Rhine wine is equivalent to five or six tablespoonfuls of an easily digested oil, but the former has the great advantage of directly increasing the activity of the organs when this is lowered, and of being simultaneously absorbed without difficulty by the lymphatics and blood.

This corresponds with our practical experience at the bedside, when wine has formed the chief or even the exclusive food, but it has nevertheless met with considerable contradiction. It could only be refuted by experiments upon HUMAN BEINGS, and by a series of investigations into the question of the changes in the inspired and expired air, both when alcohol is administered and when it is not. In 1886, Zuntz in Berlin, and Geppert in my laboratory, simultaneously investigated this important question, and came to very similar

[1] F. Strassman, 'Arch. d. ges. Physiol.,' 1891, Bd. xlix, s. 315.

conclusions; 20 to 75 c.c. of absolute alcohol taken in water, as brandy, port, or sparkling Rhine wine, by healthy adults, who were accustomed to moderate doses of alcohol, or who were abstainers, caused NO CHANGE, or very little, either one way or the other, in the quantity of oxygen inspired. The quantity of carbonic acid exhaled was either not affected or slightly diminished.

The absorption of oxygen remained always the same, a fact which is of the greatest importance. We know that alcohol, with the exception of a minute fraction, is completely oxidised in the organism; it therefore did not increase oxidation or metabolism, nor did it change the regular uniform course of the latter to a morbid and retarded one; it simply acted as a fuel for the purpose of keeping up that normal temperature of the living body, without which the whole machine would soon stop. Alcohol, when taken internally, acts in a similar way to oil or sugar. One part of the available oxygen which would otherwise serve for the oxidation of the tissues, is used up in the combustion of the alcohol, and consequently the metabolism of these tissues in the organism is lessened.

Even if the consumption of oxygen were increased by the administration of large quantities of alcohol on an empty stomach, as is stated by one author,[1] this would not alter our conclusions, for bread, when eaten, has the same result. Thus 35 to 38 grms. (about 9 to 10½ drachms) of alcohol increased the consumption of oxygen 19 per cent.; 120 to 190 grms. (about 4 to 6 oz.) of bread increased it a little over 24 per cent.

The principal thing, however, is that there is a saving of albumen. The physiology of nutrition teaches us that the WASTE OF ALBUMEN which takes place in the body is slight, so long as there is a supply of carbohydrate or of other oxidisable substances. In accordance with this we find that the normal quantity, in the urine, of the final products of the waste of albumen is DIMINISHED when moderate doses of alcohol are taken. This point, upon which all investigators now agree, has met with less contradiction than any other in the discussions as to the pharmacological action of

[1] Henri Jean, 'Bull. de l'Ac. belge,' 1883, No. 1 (quoted by Zuntz).

alcohol. Let us consider the statement of L. Riess,[1] one of the many on this subject. To a healthy man, A, were given every day 80 to 160 c.c. of diluted alcohol, whilst another, B, received 160 to 320 c.c. The chief constituents of the urine gave the following results :

Percentage of the Daily Decrease.

A. In six days :

Urea.	Uric acid.	Sulphuric acid.	Phosphoric acid.
22	11	22	34

B. In thirteen days :

Urea.	Uric acid.	Sulphuric acid.	Phosphoric acid.
15	16	2	11

The quantity of urine was always increased by the alcohol. The digestion, pulse, temperature, and general condition remained unaltered ; in case B the weight was increased by 1060 grms. in thirteen days. The diet each day was of course the same, and was strictly regulated.

The nitrogenous equilibrium was investigated by J. Munk in his experiments on dogs [2] with the following result :— "Medium doses, which had a stimulating but not a stupefying action, diminished the decomposition of albumen to as much as 6 to 7 per cent. below the normal."

Alcohol, according to all accounts, can act medicinally in three ways ; as a STIMULANT, as a NUTRIENT, and as an ANTIPYRETIC. The two former qualities are the more important.[3]

With regard to the use of alcohol as a stimulant to the activity of the intestinal canal, experience teaches us that a very moderate dose of a good strong wine often puts an end at once to simple dyspepsia with heartburn, eructation, and nausea, so long as there is no organic disease. How

[1] L. Riess, 'Zeitschr. f. klin. Med.,' 1880, Bd. ii, s. 1 ; C. A. Ewald und G. Gumlich, 'Berl. klin. Wochenschr.,' 1890, No. 44.

[2] J. Munk, "Der Einfluss des Eisens und Alkohols auf den Eiweisszerfall," 'Verhandl. d. Physiolog. Gesellsch. zu Berlin,' 1879, s. 39.

[3] For the therapeutic details and the literature see R. v. Jaksch, 'Verhandl. des 7 Congr. f. innere Med.,' Wiesbaden, 1888, ss. 86 bis 142. This communication has also been published separately.

this result is produced has not as yet been closely investigated, but we suppose that the slight irritation caused by the alcohol stimulates the secretion from the healthy gastric glands, increases the peristalsis of the stomach, and causes the pyloric orifice to open more frequently; in this manner the noxious ferments and their products may be counteracted or eliminated.

We must exercise extreme caution in the administration of alcohol in cases of genuine chronic catarrh of the stomach associated with changes in the mucous membrane; in many cases of acute dyspepsia, however, and of simple chronic debility of the stomach we may adhere to the old and venerable precept.[1]

We must not recommend alcohol as a stimulant for the nervous centres in healthy individuals, save in those cases in which sufficient rest can afterwards be taken, and no further continued effort is necessary. Alcohol belongs to those stimulating agents which have always, as an after effect, a corresponding reaction. The excitement caused by alcohol is always followed shortly afterwards by an equally great depression of the brain and spinal cord. The condition of the respiration and heart in this second stage has not, as far as I know, been closely investigated, but even if we allow that the improvement in their activity continues, the depression of the brain and the voluntary movements, is in itself a sufficient reason for rejecting alcohol as a stimulant in the case of healthy individuals.

The army authorities have also recognised this. In many countries tea or coffee has taken the place of brandy in long marches and warlike manœuvres; and the experiences of the last campaigns have justified this measure. Caffeine and caffeol stimulate without causing drowsiness as an after effect. Alcohol is nevertheless invaluable as a therapeutic stimulant where subsequent sleep is both possible and desirable. I need only remind you of its value in dangerous hæmorrhage, where it frequently saves life, and in collapse occurring in any acute illness.

[1] The apostle Paul wrote to Timothy (1st Tim., ch. v, ver. 23), "Drink no longer water, but use a little wine for thy stomach's sake and thine often infirmities."

Great caution must be observed in the use of alcohol in all forms of irritation of the KIDNEYS and urinary passages, for these are usually aggravated by its use. You will easily understand this if you bear in mind the fact, already discussed, that even healthy kidneys are irritated by moderate doses of alcohol. Where nephritis is threatened or already exists, we must, of course, be still more careful not to increase the work of the secreting epithelium of these organs.

The question whether alcohol is eliminated with the secretion of MILK is of practical importance. Lewald and Stumpf did not detect it in the milk of a goat, but R. Demme found it in the milk of a woman who was in the habit of drinking to excess.[1] A detailed investigation showed me that when 25 and 50 c.c. of absolute alcohol diluted with water were given to a goat, no trace of alcohol was found in the milk, but when 100 and 200 c.c., which completely intoxicated the animal, were administered, 0·3 per cent. were found. Two women each took 375 c.c. of a sparkling wine containing 12 per cent. of alcohol, and on a subsequent occasion 320 c.c. of a port containing 18 per cent. No appreciable amount of alcohol could afterwards be found in the milk.[2] Stumpf found, moreover, that alcohol did not increase the quantity, but that it affected the quality of the milk by increasing the relative amount of its fatty constituents.

With regard to the action of alcohol on the TEMPERATURE of the body, the above-mentioned facts can only be interpreted as being opposed to its dietetic use in general, when they are regarded from a superficial point of view. The workman, the soldier, and the sportsman seem to want, at frequent intervals, small quantities of alcohol when the air is cold. The subjective sensation of warmth in the stomach and the skin may be one reason; another may be the fact that cold increases oxidation in the body. Alcohol decreases the waste of albumen to a slight degree, and further, as combustible material, itself takes the place of a portion of the albumen, and so saves the economy. Any objective

[1] Lewald and Stumpf, loc. cit.; R. Demme, 'Der Einfluss des Alkohols auf den Organismus des Kindes,' 1891, s. 83.

[2] Klingemann, 'Arch. f. pathol. Anat.,' 1891, Bd. cxxvi, s. 72, Pharmacolog. Inst. Bonn.

change in either direction in the temperature of the body from small doses of alcohol is out of the question, especially in those individuals who are accustomed to take it moderately and regularly.

The facts are different in FEBRILE CONDITIONS. We possess a number of records, dating as far back as 1869, showing the antipyretic effect of alcohol. The English and Americans, who only regarded it as a "stimulant," to be used in stages of exhaustion accompanying febrile disorders, have become convinced of the truth that the general improvement is not only indirectly due to the alcohol, but that it probably depends largely on the decrease of fever resulting from the administration of the alcohol.

The opinion of our clinical teachers [1] may in general terms be expressed as follows :—" Alcohol in large doses increases, in an extraordinary manner, the power of resistance to septic poison." Such statements remind me of what I have observed in my own experiments. The chart on the following page, among others, exemplifies this. It shows the temperature of two young dogs of equal size, which were in a high fever resulting from the subcutaneous injection of septic matter. J. J. was left to its fate. At the times marked with *, A. A. was given, by means of an œsophageal tube, 10 c.c. of absolute alcohol diluted with water, on an empty stomach. The septic matter was injected at 3 o'clock, when the temperature taken in the rectum of J. J. was 38·6° C., and of A. A. 38·9° C.

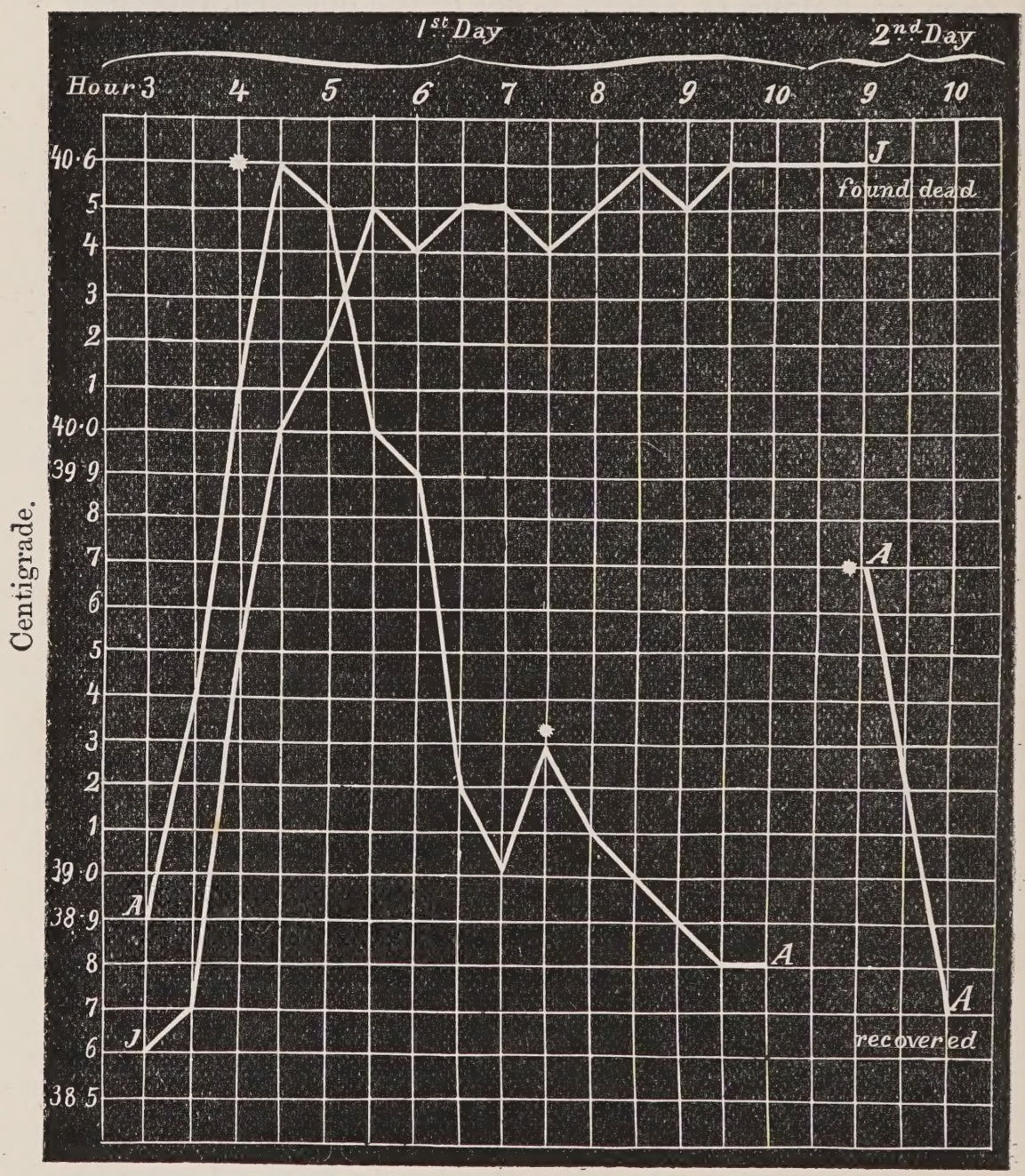
G. Strassburg,[2] when he was my assistant, made some very thorough investigations on human beings. There is hardly a fever which offers greater resistance to the action of ordinary antipyretics than the hectic fever of consumption; whilst in no other disease were physicians so much afraid of congestion, hæmorrhage, &c., being induced by the stimulating effect of alcohol.

Strassburg was allowed to treat the phthisical patients in

[1] M. Runge, "Die allgemeine Behandlung der puerperalen Sepsis," 'Arch. f. Gynäkol.,' 1887, Bd. xxx, s. 1, and 1888, Bd. xxxiii, s. 39; v. Jaksch, loc. cit., 122; A. Jacobi, 'Behandlung septischer Diphtherie,' 10 Internat. Med. Congr., 1890, sect. f. innere Med.

[2] G. Strassburg, 'Arch. f. path. Anat.,' 1874, Bd. lx, s. 471.

FIG. 29.



the military hospital at Bonn with the best brandy. The following is a report of one of the cases :—A soldier aged twenty-two, with all the symptoms of hectic fever, had 100 c.c. (3½ oz.) of brandy (= 45 c.c. of absolute alcohol) in 200 c.c. (7 oz.) of water given to him every evening, at 5 o'clock, for several days. The temperature was taken shortly before the administration of the brandy, and also an hour later. This treatment was carried out on thirty days. During this period there were twelve evenings on which

water only was given. During the first series of days on which alcohol was given, THE TEMPERATURE ON EACH OCCASION FELL, sometimes as much as 0·9° C. (1·6° F.), the average decrease being a little over 0·5° C. (0·9° F.). During the twelve days on which water only was given, no change was observed in the temperature—taken at the corresponding times—on five days; on four there was an increase of 0·3° C., and on the three others a fall of only 0·1° C.

The great difference is very evident. The alcohol administered had no injurious effect on any of the other symptoms. The patient, on the contrary, felt a pleasant sense of stimulation, slept well, and said that he perspired less at night after taking the alcohol. The fatal termination of the disease cannot be much delayed by this treatment, but the condition of the patient is improved, and it is therefore more rational to prescribe alcohol than the various kinds of insipid, watery, mucilaginous decoctions which were formerly in vogue. There is all the more reason for employing this method, when the patient has previously been accustomed to the moderate use of alcohol. The prohibition of alcohol under such circumstances, as was at one time the common practice, was, to say the least, both useless and cruel. Such methods have been discarded now almost everywhere in consequence of our researches.

The fact, first demonstrated in England by the followers of Todd, that fever patients can take large quantities of alcohol without becoming intoxicated, is of interest. If intoxication occurs, it is a sure sign that the febrile temperature has fallen to the normal, on account of the commencement of recovery. The reason of this is, probably, that a large dose of alcohol undergoes combustion more rapidly in fever, than it does when the temperature is normal and consequently only a moderate amount of oxidation is going on. Alcohol circulates longer in the latter case, and can act on the brain. This corresponds with what we see in practice —and with what is also shown in the chart given above—that the fall of temperature caused by alcohol does not last long in high fever.

How can we account for the fall of temperature when sufficiently large doses of alcohol are administered? Part

of the answer to this question is contained in the fact that it is easier to lower the temperature in warm-blooded animals when they are in a febrile condition than when they are not. The antipyretic effect must therefore depend upon some previously existing essential difference.

We can observe such a difference in the vessels of the skin,[1] which are usually greatly contracted in cases of high fever. The skin is consequently anæmic, and does not give up sufficient heat to the air in the room, which is much cooler. The heated blood remains for a longer time in the internal vessels, and is, in consequence, less frequently cooled than when it comes to the surface. Alcohol changes all this. A few minutes after its administration the skin becomes warmer, and remains so for some time, and this is more strongly marked the larger the dose.[2]

This increased transference of blood from the internal parts of the body to its surface is further assisted by the increased activity of the heart. It is well known that it is precisely the "adynamic" type of fever, with a very feeble pulse, which is especially benefited by the administration of alcohol.

The presence of noxious ferments in the body of a fever patient, and the morbid increase of the cellular activity to which they give rise, constitute another of the differences referred to above. We can have no further doubt, considering the figures previously given in this lecture, that alcohol, even in non-poisonous doses, exercises a depressing influence on the assimilating cells. I have experimentally demonstrated that this influence is not dependent upon the brain or the vaso-motor nerves.[3] I divided the cervical cord of large dogs, whilst deeply narcotised by ether, between the sixth and the seventh vertebræ, then wrapped the animals up in cotton wool and put them in a warmed room. The temperature rises very rapidly under these circumstances. The animal dies several hours later,

[1] E. T. Reichert, 'Therap. Gazette,' 1890, February 15th.

[2] Ch. Wershoven, 'Der Einfluss des Weingeistes auf die menschliche Haut hinsichtlich d. Wasserverdunstung u. d. Wärmeabgabe,' Bonn, 1885.

[3] C. Binz, 'Arch. f. pathol. Anat.,' 1870, Bd. li, s. 6.

with a temperature of over 41° C. (105·8° F.), whilst the TEMPERATURE RISES AFTER DEATH to a point as high as any recorded in the most malignant infectious fevers. Two control experiments, which I purposely made, corroborate this fact, if any doubt were left. The heat-regulating apparatus, with the exception of that controlling the head and neck, is cut off in this preliminary experiment; the transversely striated muscles, which are of such importance in regulating the temperature, are completely paralysed with the exception of the diaphragm, the heart, and the comparatively small number attached to the head; the arteries of the trunk and limbs are dilated to their utmost extent; the amount of heat lost on account of the hyperæmia of the skin is as large as it can be; a further increase in this respect can hardly be imagined, and is rendered almost impossible by the nature of the experiment. Yet we may observe as clearly here, as in any other case, that alcohol, when given in non-poisonous doses, lowers the temperature; and that the POST-MORTEM increase of temperature, which depends upon a purely chemical process, and which amounted in the control experiments to 1·5° and 0·9° C. (2·7° and 1·6° F.), is prevented by the action of the alcohol.

Other conditions which lower the temperature, by acting upon the nerve-centres, are not excluded. It is, for instance, quite possible that alcohol taken in a large quantity of water quickly eliminates, by its strong diuretic action, the bacterial products which set up fever and paralyse the nerves.

The PREPARATIONS of alcohol require, on the part of the physician, a much more careful and thorough investigation than has hitherto been given to them. If healthy individuals experience ill effects from drinking bad or adulterated spirits, how can we expect patients to recover when treated with them?

The SPIRITUS of the German Pharmacopœia is a liquid which

contains about 90 to 91 per cent. of absolute alcohol with nine or ten parts of water.[1] It should be free from fusel oil —that is to say, when a little is rubbed on the hand no trace of the well-known unpleasant smell, which is a peculiar characteristic of the homologous but less volatile alcohols, should be detected. The following is a very sensitive test. Evaporate 50 c.c. of the spirit with 1 c.c. of caustic potash down to 5 c.c., and saturate the residue with dilute sulphuric acid. No odour of fusel oil should be developed by the process.

Spiritus Dilutus is spirit which is diluted with water, and contains about 68—69 per cent. of absolute alcohol.[2]

The different kinds of ardent spirits contain, as a rule, 40—60 per cent. of absolute alcohol, the rest being chiefly water. They also contain, according to the source from which they are derived, various unimportant colouring matters, and each possesses its peculiar aroma. Only the better class of spirits, possessing some age, should be given to patients. Among these may be included old well-seasoned whisky made from barley, rum prepared from cane-sugar, arrack prepared from rice or cocoa-nut juice, and brandy distilled from wine. The "bouquet" is due to the presence of certain compound ethers belonging to the fatty series. In rum, butyric ether preponderates; in brandy, acetic, caprylic, and capric ethers. Spurious imitations of the various liquors are made by adding these ethers, with the requisite quantity of water and a little burnt sugar, to home-made potato spirit; this is done to such an extent, that these artificial products ought never to be employed in the sick room.

The natural ethereal compounds present in spirits possessing an agreeable bouquet, certainly have a stimulating effect on the nervous system, which is very useful under certain circumstances. The new German Pharmacopœia calls brandy Spiritus e Vino, and requires it to contain 46 to 50 per cent. by weight of alcohol.[3]

[1] The Spiritus Rectificatus (Ph. B.) contains 84 per cent. of absolute alcohol.—*Transl.*

[2] Spiritus Tenuior (Ph. B.) contains 57 per cent. by volume of absolute alcohol.—*Transl.*

[3] Anhydrous alcohol has a sp. gr. 0·793, and therefore 8 per cent. by weight is approximately equivalent to 10 per cent. by volume.

The characters of WINES differ so greatly that we can only refer here to those which are common to all. They contain from 5 to 20 per cent. by volume of alcohol, a large quantity of water, the salts of their respective fruits, free acids, ethereal compounds, together with some glycerine and colouring matter; the stronger kinds also contain sugar. The better kinds of German wines contain 8 to 11 per cent. by volume of alcohol, claret about the same, and champagne a little more. The selection of a particular wine depends altogether on the indications present—whether, for instance, a large amount of tannin, vegetable acid, aroma, or alcohol is desirable, or the reverse. Turbid or very new wine should not be given to patients under any circumstances, neither should any concocted beverage, nor one adulterated with all kinds of additions, such as impure glucose to the "must," nor one which has been "improved" by the addition of glycerine, potato spirit, or artificial ethereal compounds. Chemical science has not as yet advanced sufficiently far to provide a good substitute for the products of nature.

Most red wines contain a large amount of tannic acid, derived from the skin of the grapes, and it may be due to the presence of this substance that, as observed in a bacteriological research,[1] the number of micro-organisms in the fæces decreases considerably after the administration of 1 litre of red wine, but not after the same quantity of white wine.

The physician himself will rarely be in a position to test the purity of the wines. The wine "from the juice of grapes" is, in fact, officinal in Germany, in order that the physician may be able to prescribe a wine, suitable for therapeutic purposes, even in districts where none is produced. The German Pharmacopœia does not, however, give any of the recognised tests for inferior quality or gross adulteration[2] of wine, and so the single qualification above mentioned as to its origin is the only protection we have against the

[1] W. Sucksdorff, 'Arch. f. Hygiene,' 1886, Bd. iv, s. 355.

[2] Since the 1st of April, 1895, when the new appendices came into force, this state of matters has been improved.

druggist sending cider, perry, &c., when "wine" has been ordered for the patient.

To supply to some extent the omission with regard, at least, to RED WINE, I will here, by a few simple tests, show you how easy it is to detect any adulteration. This wine, on account of the considerable decline in its production in France, is now more adulterated than any other, by adding colouring matter to white wine, or to mixtures resembling wine.

If a natural red wine is mixed with half its quantity of solution of ammonia in a test-tube the colour at once turns to a dirty green; a wine coloured with fuchsine, however, becomes colourless, but regains its bright red colour if acetic acid is afterwards added in excess. The natural colouring matter does not change at first on the addition of solution of copper sulphate, but gradually it turns brown. On the other hand, the colouring matter of the bilberry (*Vaccinium myrtillus*) changes to a beautiful violet, the colouring matter of the garden mallow (*Malva arborea*) becomes deep blue, whilst that of the scarlet berry (*Phytolacca decandra*) is first changed into a dark brown and then into a greenish colour.[1]

Although some of these substances, such as the bilberry and the mallow blossom, are perfectly harmless when used for the artificial colouring of wine, still their presence makes it incumbent on the physician to reject the wine on the ground that it is not a natural, but an artificial or adulterated wine. The tests, however, must be applied very carefully and with every precaution, otherwise inferior, but nevertheless genuine, wines may be supposed to be adulterated.

SPARKLING WINES have a refreshing effect on account of the large amount of carbonic acid they contain, and may be advantageously employed in certain forms of impaired digestion, as they are absorbed into the system more rapidly than other wines.

There are numerous reports as to the mode in which a sound natural wine, which is also relished by the patient, may prove of service. Here is one, which also includes a few practical hints about the quality of the wine. "The

[1] For a detailed account see J. König, 'Die menschlichen Nahrungs- und Genussmittel,' 1883, vol. ii, s. 572.

result which others try to produce (in the treatment of puerperal fever) by digitalis, quinine, and sodium salicylate, we obtain by prescribing a diet which is easily digested, liquid and nutritious, together with large quantities of wine. . . . The latter must be very strong, and not too sweet, so that it may be taken for a considerable period; neither must it be so acid as to have a perceptible effect on the peristalsis of the intestines. I now always prescribe a very strong Spanish wine, which can be taken in large quantities. Most patients drink it undiluted, and take, if it is necessary, as much as one litre (36 ounces), and even more, daily.[1]

Beer, also, is therapeutically an important alcoholic beverage. Let us consider, from a medical point of view, the characters of the two kinds from Munich and Vienna respectively—the consumption of which throughout the world is probably larger than that of any other variety. These contain from 3 to 5 per cent. of alcohol, in addition to extract of hop and carbonic acid. The latter substances frequently, by their special effects, increase the medicinal value of alcohol. The presence of derivatives of starch, of phosphates, and of albumen, is of importance on account of their nutritive value. Munich beer contains from 2·7 to 5·6 per cent. of albumen. It is peptonised in the malting process, and thus can be directly absorbed by the stomach.[2]

Even now we sometimes hear appeals made to the authority of Liebig, who stated in his 'Letters on Chemistry,' 1852, p. 387, that a pinch of flour is more nourishing than five quarts of the best Bavarian beer; that a man who drinks five quarts of beer daily can only reckon at the end of the year on having consumed the equivalent of a five-pound loaf, or three pounds of meat. Liebig omitted this statement in the later edition (1859), and even what he says there about the action of alcohol on the organism might, with the exception of the sentence "as regards its respiratory value, alcohol comes next to fat," have been also omitted with advantage.

[1] F. Ahlfeld, 'Berichte und Arbeiten aus der gynäkol. Klinik,' zu Giessen, 1883, s. 226.

[2] E. Sell, "Ueber Bier und seine Verfälschungen," 'Deutsche Vierteljahrschrift f. öffentl. Gesundheitspflege,' 1878, Bd. x, s. 1.

Alcohol can cause three forms of POISONING,[1] which differ greatly in their clinical aspect—acute intoxication, chronic alcoholism, and acute delirium tremens. I shall only briefly discuss the two former kinds; the third belongs to clinical medicine.

INTOXICATION is a commencing or complete paralysis of the brain-cells caused by alcohol or the products of its oxidation. It may—even in cases which do not end fatally—be so considerable that we are unable to obtain any muscular reaction by stimulating the cerebral cortex with the intermittent current.[2] I will here give you some facts as to the BLOOD-PRESSURE in acute alcoholism, which I obtained in investigating the effects of stimulants on dogs. In these experiments the narcosis from the amount of alcohol administered was so profound, that the animals gave no sign of sensibility whatever, whilst their carotids were being prepared. The arterial pressure of a healthy dog amounts to 100—140 mm. of mercury. I saw it fall to 70 mm. after the administration of an amount of alcohol which was insufficient to endanger life. This is certainly one reason why people in a state of complete intoxication often appear cyanotic.

The decline in the TEMPERATURE of the body, which follows the combined action of alcohol and considerable external cold, is astonishing. Magnan reports that the (rectal) temperature of a woman who had been thoroughly chilled, and who was in the habit of drinking, fell to 26° C. (78·8° F.). The patient recovered within eight hours, in so far that her temperature rose to 37° C. (98·6° F.) and remained at that point.[3] A number of cases were collected in Hamburg, among which was that of a drunkard of thirty-four, who was taken to the hospital in February, after spending the night in the open air. The rectal temperature in this case was 24° C. (75·2° F.). Ten hours afterwards it had only reached 32·6° C. (90·68° F.), whilst it did not return to the normal until twenty-four hours had elapsed.[4]

[1] H. Baer, 'Der Alkoholismus,' Berlin, 1878; also 'Die Trunksucht und ihre Abwehr,' Wien und Leipzig, 1890.

[2] St. Danillo, 'Arch. de Physiol.,' 1882, vol. x, p. 388.

[3] Magnan, 'Gazette méd. de Paris,' 1870, p. 88.

[4] Reincke, 'Beobachtungen über die Körpertemperatur Betrunk-

A great difference between the temperature of the body and that of the air is in itself sufficient to cause a great loss of heat. The organism compensates for this loss, up to a certain point, by increasing its oxidation. This is the reflex consequence of the stimulation of the peripheral nerves by the cold. Alcohol in large doses paralyses the reflex apparatus, and consequently the capability for regulating the heat of the body. Moreover as a result of the action of alcohol on the activity of the cells, a diminution of the different oxidation processes sets in, whilst the blood-vessels of the skin, through which the loss of heat takes place, are at the same time relaxed. Thus the deficient controlling power, the unchecked dissipation of heat, and the diminished oxidation, all act in the same way. It has been asserted that the low temperature results entirely from the increased dissipation of heat; but this appears improbable if we consider the fact that it takes hours, in individuals under the influence of alcohol, before the temperature rises again, even when the loss of heat is prevented as much as possible by enveloping them in the most complete non-conductors.

In cases of acute poisoning by alcohol, where life is prolonged for some days, changes may take place in the skin exactly similar to those which arise from bruises and burns:[1] extravasation of blood extending even into the muscles, œdema of the cellular tissue, dark red spots with separation of the epidermis, blisters which are localised or affect large areas, and gangrene—in short, all the symptoms of burns of a slight or severe character. These symptoms are most strongly marked in those parts which are exposed to pressure from the recumbent posture of the patient. They offer, on the whole, the appearances which are seen in scurvy and its sequelæ. Serous exudations occurring in the meninges and cavities of the brain and in the pericardium make this resemblance complete.

The treatment of acute alcoholic narcosis, if the condition

ener,' 1875, Bd. xvi, s. 12; H. Weckerling, ibid., 1877, Bd. xix, s. 317.

[1] A. Mitscherlich, 'Arch. f. path. Anat.,' 1867, Bd. xxxviii, s. 319; Heinrich, 'Vierteljahrschr. f. gerichtl. Med.,' 1868, Bd. ix, s. 359.

is not too pronounced, resolves itself into an expectant one. Alcohol is the least harmful of all the ordinary narcotics. Prompt treatment is, however, necessary when the temperature of the body continues to fall, when the respiration and pulse grow feebler and less frequent, and when the cyanosis of the lips and the pallor of the face are increasing. Such measures must be adopted as I have already described in detail.

CHRONIC ALCOHOLISM is mostly met with in the colder climates. The need for taking alcohol is felt less in the warmer countries of the south, since a warm temperature does not affect the metabolism of the organism so quickly as a cold one does. Naturally, therefore, the desire for something which will check the metabolism is less strongly felt, and the Koran is not wrong in forbidding the use of wine by the Orientals. Europeans who wish to preserve their health in India must modify essentially their mode of living, if they have previously been accustomed to take strong alcoholic drinks. But in countries where the waste of combustible material is much larger, owing to the continued stimulation of our metabolism by the colder external air, it will perhaps be a vain endeavour to try to put an end to the use of alcohol. All that can be done is to render it less necessary to the great mass of the population, by the introduction of better conditions of existence; by bringing its use within reasonable limits by means of legal and legislative measures; by insisting upon improvements in the methods of purification; by encouraging the production of light wines and of malt liquors; and by restricting the sale of all strong alcoholic beverages by granting monopolies and imposing heavy duties.

Chronic catarrh of the digestive tract with all its consequences, fatty degeneration of the glandular organs and the heart, dilatation of the small vessels, and atheromatous degeneration of the larger ones, Bright's disease of the kidneys, cirrhosis of the liver, atrophy of the retina, chronic pachymeningitis, and various brain affections, are the chief disorders resulting from the continual abuse of alcohol. Although it may be useful under certain conditions, as a food, it is not an innocuous substance like sugar or starch, but

always acts on the tissues as a foreign irritant, and sets up some morbid action unless its use is kept within very strict limits. It has been observed in dogs that moderate doses of alcohol, which stimulate but do not intoxicate, diminish the waste of albumen, as estimated by the nitrogen in the urine and fæces, from 6 to 7 per cent.; whilst doses which cause intoxication INCREASE the waste from 4 to 10 per cent.[1]

It has been pointed out that chronic alcoholism is developed sooner and more readily by ordinary spirits if they contain a large amount of the secondary products of distillation. In addition to ethyl alcohol, a series of other compounds is developed in the fermentation and distillation. Many of these are well known, but others have escaped analysis, either from the difficulty of isolating them, or from their volatile nature, or from the small quantity present. Those which are known comprise the higher alcohols of the fatty series, the fatty ethers of many of these alcohols, and some volatile bases of the pyridine series.

Fusel oil, and its chief constituent, amyl alcohol, have naturally received most attention in the investigation of the action of these bodies upon the organism. For it has a disagreeable taste and smell, which are very noticeable even when it is largely diluted, and almost everything which has a disagreeable smell is injurious to human beings.

The first investigation of this subject, so far as I know, was that of Pelletan's in 1825. Since that time many experimental investigations of the question have been carried out and many papers published. The majority of the investigators have come to the conclusion that amyl alcohol is much more poisonous than ethyl alcohol, and they consider that its presence in the commercial spirits of northern countries renders them extremely injurious. The minority consider that these two statements are, to say the least, unproved.

Sten-Stenberg,[2] in opposition to the statements of Dujardin-

[1] J. Munk, 'Verhandlungen d. Physiol. Gesellsch.,' zu Berlin, 1879, 3 Jan.; C. v. Noorden und O. Peschel, des letzteren Doctordiss., Berlin, 1890, s. 28.

[2] Sten-Stenberg, 'Arch. f. exper. Path. u. Pharmak.,' 1879, Bd. x, s. 356.

Beaumetz, obtained negative results with a mixture of pure spirit and amyl alcohol. He, however, only experimented with rabbits, and it is well known that there is hardly any warm-blooded animal which is so refractory to other narcotics (atropine, morphine) as the tame rabbit. The cerebral cortex of this animal reacts very sluggishly.

We see striking results in every-day life of the action, on the brain, of the so-called pure and of the impure or unripe alcoholic beverages. Anyone who is in the habit of drinking several glasses of some spirituous beverage knows that the after effects of old wine or brandy, especially when this is distilled from matured natural wine, are very insignificant. New wine, even when it is quite clear, and still more, recently distilled spirit, even of the best quality, produce an excited, confused, and stupid condition of the brain, without causing any previous intoxication.

The disagreeable effects which are experienced, are certainly not due to the presence of a larger quantity of ethyl alcohol. I have estimated the amount of spirit present, and I am convinced that it is not greater than what is found in perfectly harmless wines. Again, there may be no digestive derangement at all. The disagreeable effects are due to the intermediate and accidental products, which during the "ripening" of the beverage slowly disappear, undergo oxidation, or form harmless compounds. The oxygen of the air continually gains entrance through the pores of the casks, or is enclosed in the bottles when the liquor is poured into them (the coefficient of absorption of alcohol for oxygen is, at 15° C., nearly ten times greater than that of water, the figures being 0·283 and 0·030). Volatile bodies are dissipated through the cask; the aldehydes,[1] which strongly affect the brain, are oxidised, and the resulting acids combine with the alcohols, and gradually form the so-called "bouquet," which has so agreeable and pleasant an effect upon the system.

C. Brockhaus,[2] of Godesberg, investigated this subject,

[1] N. P. Hamberg, ref. 'Jahrb. d. ges. Med.,' 1884, Bd. cci, s. 27.

[2] Brockhaus, "Studien über die Giftigkeit der Verunreinigungen des Kartoffelbranntweins," 'Centrabl. f. offentl. Gesundheitspflege,' Bonn, 1882, s. 146. This exhaustive and painstaking work, carried out in the Bonn Pharmacological Institute, was omitted by an oversight of mine rom the 'Uebersicht über die Arbeiten deutscher Pharmakologen aus

and came to the conclusion that the effects, on the human subject, of the collateral products of distillation are "incomparably more powerful" than that of ethyl alcohol. Although as much as 120 grammes (about 4 ounces) or more of the latter could be taken, when largely diluted, without unpleasant results, still, unpleasant effects, differing in degree according to the substance employed, were produced if small quantities of these collateral products were added to the beverage. The symptoms most generally observed were, irritation of the mucous membrane of the respiratory and digestive organs; smarting of the lips, tongue, pharynx, and throat; a tendency to cough and sneeze; a feeling of oppression and constriction in the chest; pain and a sensation of burning in the stomach, together with nausea; disturbed action of the heart, palpitation, congestion of the head; general constitutional disturbance with languor and heaviness of the limbs; finally, irritability of the nervous system and brain, as shown by headache, giddiness, confusion of the mind, or a feeling of intoxication. These symptoms were most strongly marked after taking aldehyde (C_2H_4O) and amyl alcohol ($C_5H_{12}O$), and least after propyl alcohol (C_3H_8O); acetal ($C_6H_{14}O_2$) and isobutyl alcohol ($C_4H_{10}O$) occupied an intermediate position.

Experiments[1] recently carried out on dogs have, on the whole, corroborated this poisonous action of amyl alcohol. The addition of 1 per cent. of this to the alcohol given in the food intensified some of the symptoms; with an addition of 3 per cent. the symptoms became still more pronounced, and brought about the death of the animal in less than half the time which elapsed when no amyl alcohol was given. We may conclude from these experiments that, as the human brain is more sensitive than that of the dog, quantities smaller than 1 per cent. of amyl alcohol added to ordinary spirit will, if repeatedly taken, produce deleterious effects.

den Jahren 1865—1889, published by Binz, Boehm, and Liebreich, Berlin, 1890, and edited by Dr. A. Würzburg.—A. Baer, "Die Verunreinigungen des Trinkbranntweins insbesondere im hygienischer Beziehung," 'Centralbl. f. allgem. Gesundheitspflege,' Bonn, 1885, s. 278.

[1] F. Strassmann, "Experimentelle Untersuchungen zur Lehre vom chronischen Alcoholismus," 'Vierteljahrschr. f. gerichtl. Med.,' 1888, Bd. xlix, s. 232.

According to another view, based in some measure on certain experiments on men, the small quantity (such, for instance, as 0·3 to 0·4 per cent.) of fusel oil contained in spirituous liquors does not have the injurious effect ascribed to it. The whole subject with regard to human beings evidently requires further investigation, and the observations should extend over a considerable period. The task will certainly not be an easy one.

Many things, in my opinion, point to the probability that the reason why old well-seasoned wines, with a rich bouquet, have comparatively little injurious effect upon the brain is that the action of the alcohol is modified by the aroma. I can easily imagine that this corrective effect is similar to that which is produced by very small doses of atropine on certain collateral effects of large doses of morphine.

I cannot close this chapter without expressing my conviction that a healthy and well-nourished individual has no necessity for alcohol at any time or in any form, and that the practice of drinking strong alcoholic liquors by such a person cannot be too strongly condemned.

Let me add to this the earnest hope that physicians will, when prescribing alcohol, take every care as to the conditions under which it is administered, lest the patient, whilst recovering from one disease, should contract another, scarcely less disastrous—a continuous craving for stimulants.

XVI.

The ethereal or essential oils—Their origin, properties, classification, composition—Camphor—Experiments upon human beings and warm-blooded animals—Antiseptic properties—Antipyretic action of camphor—Stimulation of the heart and respiration—Secretion of saliva and perspiration—Preparations — Camphoric acid—Turpentine — Turpine hydrate—Sedative action of the ethereal oils upon the nervous system—The Pharmacopœial preparations of the ethereal oils and other allied drugs.

The perfume of many plants gave rise to the idea that they possessed medicinal virtues, and they were consequently employed as remedies. Experience justifies us in the belief that anything which is pleasant and agreeable to our sense of smell may be considered to be beneficial, or at least harmless, when taken in moderation. Plants of this kind, and substances derived from them, are among the oldest and most generally employed remedies. The Egyptians and Greeks wrote about their use, and the Pharmacopœia of the present day contains a goodly number, in spite of the fact that many of them have been discarded during the last hundred years.

The principal substances derived from these plants have an oily appearance, and are easily volatilised when distilled with water. They are called oils, as they somewhat resemble externally the fatty oils, but they differ widely from the latter in their chemical properties. As you see from the examples placed before you, (1) they have the consistence of the fatty oils, some being even as viscid as castor oil, especially when they have become somewhat resinous through oxidation; (2) they are like the fatty oils, apparently at least, in their insolubility in water; (3) they are mostly lighter than water, and therefore float on the top of it; (4) they are easily

soluble in ether, chloroform, and in the fatty oils; (5) they make the well-known greasy spot on paper, which differs from that made by the fatty oils only in that it disappears, owing to the volatilisation of the non-resinous portion.

They are obtained by finely dividing those portions of the plants which contain the oil, and then subjecting them to pressure. They are also obtained from the plants by extraction with hot oil or by distillation with water, or by treating the vegetable substance with superheated steam, which facilitates the volatilisation of the oil, although it has a higher boiling-point than water. The process in which the same hot water charged with the oil is redistilled several times with fresh portions of the plants, until the quantity of the oil which comes over exceeds the solvent power of the water, is called cohobation.

The largest quantity of these oils is yielded by the *Umbelliferæ, Labiatæ, Aurantieæ, Abieteæ,* and a few specimens of the *Synanthereæ:* the *Cryptogamiæ* contain none. They are frequently found in special, small, round cavities in the cellular tissue of the so-called oil glands, and may often be seen distinctly with the naked eye—as, for example, in the rind of the orange tribe, or in the leaves of the *Eucalyptus globulus.* From a physiological point of view the ethereal oils, like the alkaloids, are excreta formed in the metabolism, and are no longer necessary for the life or preservation of the plants; their perfume, however, attracts insects to the plant, and in this way the oils are of service in promoting the fertilisation of the flowers.

Many of them solidify at the ordinary temperature. Consequently they have been divided pharmaceutically into two classes in accordance with a suggestion of Berzelius: the Elæoptenes (from ἔλαιον and πτηνός = oil and volatile), and the Stearoptenes (from στέαρ = tallow). The latter are crystalline bodies, and have the generic name of camphor.

The ethereal oils have no uniform chemical composition. They may or may not contain oxygen, and in some cases—*Cruciferæ* and *Asafœtida*—they also contain sulphur and cyanogen compounds.[1]

[1] Some contain alkaloids, see P. Pellacani, 'Arch. f. Path. und Pharmak.,' 1883, Bd. xvi, s. 440.

Those which contain no oxygen belong chiefly to a particular class of hydrocarbons, the Terpenes ($C_{10}H_{16}$), and are further subdivided into groups according to their physical properties (boiling-point, polarising and refractive powers), and their chemical characters[1] (formation of halogen compounds). Of those which contain oxygen, some—for example, camphor and eucalyptol—are allied to the terpenes; others, as oil of cinnamon, to the aldehydes, or, as oil of winter-green, to the ethereal compounds; or they may be compounds belonging to the fatty or aromatic series.

The ethereal oils are slowly oxidised on exposure to light or air, and thereby become coloured, if not so already, and viscid; that is to say, they assume the character of RESINS. Carbonic acid, the acids of the methane series, and especially of the resins—constituting the greater portion of the resins—are formed in this process. The name BALSAM is given to the viscid substance which is intermediate between the oils and the resins; it is really a solution of resin in an ethereal oil which is not yet oxidised. The tendency of this substance also to undergo oxidation is shown by the fact that all the balsams are quickly converted into resins when mixed with chlorine or bromine; that many give out heat and explode when brought in contact with powdered iodine, and that others burst into flame with a copious evolution of gas when treated with concentrated or fuming nitric acid. This is the case chiefly with the oils which contain no oxygen.

With regard to the behaviour of these oils in the animal body, I may make the general statement that they pass fairly quickly from the intestinal canal and subcutaneous cellular tissue into the circulation, that they may be detected by their odour in the breath,[2] and that they reappear in the urine either unchanged, or as resins, or combined with other substances.

Cold water dissolves sufficient quantities of these bodies to acquire their odour and taste, and in this way the AQUÆ of the Pharmacopœia are formed, which bear the names of

[1] With regard to the chemical details see Wallach's papers which commenced in the 'Annal. der Chemie,' 1884, Bd. ccv, s. 291.

[2] F. Tiedemann, "Die Ausdünstung in den Lungen, durch Versuche erläutert.," 'Zeitschr. f. Physiologie,' 1833, Bd. v, s. 203.

the respective plants. They are prepared either by distillation or by adding a few drops of the oil to a litre of water and thoroughly agitating it.

The more expensive kinds of ethereal oils are frequently adulterated, usually by the addition of oil of turpentine.

In discussing the remedies belonging to this group I will direct your attention, first of all, to the one which is most frequently employed and has been most closely studied, namely, CAMPHOR. This is contained in all parts, but more especially in the wood, of the *Cinnamomum camphora*, a large tree belonging to the Natural Order Laurineæ, growing in China, Cochin-China, and Japan, but principally in the island of Formosa, where there are whole forests of it. The camphor is obtained from the wood by first cutting it into chips, and then exposing these to the vapour of boiling water; the camphor volatilises with the steam, and is then collected, and repeatedly sublimed in order to free it from the various impurities.

It is a white, crystalline, friable substance, which readily burns with a smoky flame. It soon volatilises, when put in an open flask, without leaving any residue, and is deposited in the upper part of the flask in shining hexagonal crystals. It can be reduced to a state of powder by moistening it with some solvent. Its composition is $C_{10}H_{16}O$. I shall again refer to this formula when I discuss menthol.

The camphor which is now officinal was first brought to Europe by the Dutch in 1641. Previous to that the camphor from Borneo[1] had been used in medicine from the sixth century, but subsequently this was replaced by the cheaper variety obtained from the camphor laurel.

Numerous experiments, both upon individuals and upon animals, have been made during the last two centuries.

W. Alexander, after taking a single dose of 40 grains in a little syrup, experienced the following effects:[2] lassitude, depression of spirit, giddiness, a feeling of suffocation, unconsciousness, STRONG CONVULSIONS with foaming at the mouth, a sensation of external heat, and increased heat of the skin

[1] Flückiger, 'N. Repert. für Pharmacie,' 1868, Bd. xvii, s, 28; J. Moeller, 'Lehrbuch der Pharmakogn.,' 1889, s. 382.

[2] W. Alexander, 'Experimental Essays,' p. 128, London, 1768.

as shown by the thermometer. At the end of three hours, after drinking large quantities of warm water, he vomited the greater part of the camphor undissolved in the water. The most serious symptoms were then relieved, but the giddiness and headache continued for some hours. Jörg[1] and his pupils also experimented with camphor, taking doses of 11 grains (0·73 gramme). These had at first a stimulating and later a depressing effect upon the brain, and also increased the action of the heart and the activity of the intestines, kidneys, and sexual organs.

The physiologist Purkinje[2] accustomed himself to small doses of camphor, and then took a single dose of 2·4 grammes (36 grains) early in the morning on an empty stomach. He describes his experiences almost as follows:—"I was soon driven out of my bed by a restless feeling in the muscles. All movements of my limbs were greatly facilitated; when I walked my thighs were raised abnormally high, but there was no change in my muscular strength as measured by moving things out of my way. The sensibility of the skin and of the motor nerves seemed to be somewhat blunted. This was followed by a 'whirlwind of thought,' which became so intense that I thought I should lose my reason." Vomiting was induced by repeatedly tickling the root of the tongue, and Purkinje partially recovered his senses. This condition lasted for four hours. A feeling of oppressive heat spread over his head and body, and Purkinje then lost consciousness. His face became red, he fell down, the muscles being convulsed. He was put to bed, and lay there for half an hour, unconscious and breathing slowly. "When I awoke it took me a long time to find out where I was, and to get a right idea of time and space; the morning and night seemed to be a blank, what had happened could only be dimly recalled whilst I endeavoured to realise my identity. Otherwise I felt quite well, and free from that feeling of exhaustion which is so common after the use of other intoxicants. . . . . The transitory action of camphor was thereby exemplified."

[1] Loc. cit., s. 230.

[2] Purkinje, 'Einige Beiträge zur physiologischen Pharmakologie.' Neue Sammlungen auf dem Gebiet der Heilkunde, Breslau, 1829, s. 430.

Similar experiences have frequently been recorded in cases of accidental poisoning. A young healthy woman took 2 grammes (30 grains) by mistake. She soon became giddy, and six hours later she complained of headache, a sensation of burning in the stomach, and formication in the limbs. There was no loss of consciousness. Her hands were blue and cold, her breath smelt of camphor, her pulse was small and irregular, 90 to 100 in the minute ; her whole body, but especially her face, was convulsed and trembling. She was able, however, to walk, though with difficulty. The more severe symptoms disappeared in about twenty-four hours.[1]

A woman, fifty-two years old, obtained from a chemist, instead of castor oil, an ounce (30 grammes) of what is simply described as a solution of camphor in fatty oil, and drank the whole of it. She was seized with violent delirium, twitching of the facial muscles, vomiting, dyspnœa, and a feeling of cold in her limbs, which were in reality warm. Her pulse was frequent and strong.[2] The symptoms quickly subsided.

On giving moderately-sized dogs 1 to 2 grms. (15 to 30 grains) of camphor dissolved in a fatty oil, either by the stomach or subcutaneously, we notice that the animals soon become restless, and that this condition is followed by general epileptiform convulsions, which last on the average for two minutes. These commence in the face and then spread to the muscles of the trunk and limbs ; they are at first of a clonic and then of a tonic character ; they do not last long, but may recur one or more times after an interval of rest ; they gradually disappear if the dose has been comparatively small, but they quickly merge into paralysis if too much has been administered. Nothing characteristic is revealed by a post-mortem examination.

These convulsions originate in the spasm centres of the brain and medulla oblongata, and not, as is the case with strychnine, in the spinal cord. They are limited to the face when the dose of camphor is relatively small ;[3] and they still

[1] Klingelhöffer, ' Berl. klin. Wochenschr.,' 1873, s. 414.

[2] H. B. Hewetson, ' Lancet,' 1880, vol. i, p. 88 ; R. Davis, ' Brit. Med. Journ.,' 1887, vol. i, p. 726 ; death of a three-year-old child after taking 30 grains of camphor.

[3] C. Binz, "Ueber einige Wirkungen ætherischer Oele," ' Arch. f. exper. Path. u. Pharmak.,' 1875, Bd. v, s. 113.

occur even when the spinal cord is cut off from the medulla oblongata, provided that artificial respiration is kept up. This has also been observed, though naturally without the aid of artificial respiration, in the case of the frog. The convulsions, notwithstanding their severity, do not cause suffocation from tonic spasm of the diaphragm. This is one of the many points in which they resemble the convulsions of epilepsy.

It seems to me that in considering the effects of camphor on the organism, we had better keep to the facts which have been gained from clinical experience. This is considerably in advance of scientific investigations, and, so to speak, offers a sketch or outline, the details of which may be filled in by future investigations.

Camphor was employed in the first place because of its ANTISEPTIC properties, and has been used on this account for medicinal and other purposes from a very early period. This antiseptic property depends on the fact that camphor has a poisonous action upon the lower forms of protoplasm; all forms of life in putrefying fluids are paralysed and discoloured by it, though unquestionably this action is of a more transitory character than is the case with other antiseptics. Camphor has a similar action upon the leucocytes of human blood.

This paralysing action on the cells may perhaps explain how certain other results are produced. An old and well-tried method for suppressing the secretion of milk consists in putting some cotton wool, which has been saturated with an alcoholic solution of camphor, upon the breasts. The volatile stearoptene may possibly penetrate the skin, and be brought in contact with the lobules of the gland. We may also imagine that the fact that the local application of camphor sometimes checks COMMENCING suppurations, depends upon this antiseptic power. The migration of the white corpuscles into the cutaneous tissue is either diminished or entirely suppressed, whilst the other symptoms of inflammation—the redness, swelling, and heat—disappear when the cause is removed.

Pirogoff[1] says, "The effect of camphor in erysipelas of the head, is absolutely marvellous. Anyone who stood for the first time by the bedside of a patient suffering from this

[1] Pirogoff, 'Klinische Chirurgie,' Leipzig, 1854, s. 25.

affection, would be convinced that in no other disease could bloodletting be so imperatively required. . . . The red and swollen face, the great congestion of the head, the hurried and laboured respiration ; the full, hard, hammering pulse ; the hot, dry skin. . . . Six or seven doses of 0·12 gramme (1¾ grains) of camphor produce an astonishing change. The pulse becomes small and less rapid ; the skin cool, soft, and bathed with perspiration ; the extremities cool and the respiration easy."

A similar action has been observed in the SEPTIC FEVERS of animals. My pupils Kyll and Baum[1] have both published the results of experiments which show that fever in warm-blooded animals can be lessened by means of subcutaneous injections of camphor. I will call your attention to only one of their numerous charts ; the others all show the same result. This chart (Fig. 30, page 357) shows the temperatures of two large rabbits of the same age, to each of which was given, at a quarter past eleven, a subcutaneous injection of 0·5 c.c. (about 8 drops) of a liquid typhoid evacuation, one of the rabbits having 0·1 gramme (1½ grains) of camphor, dissolved in sweet oil of almonds, injected at the same time.

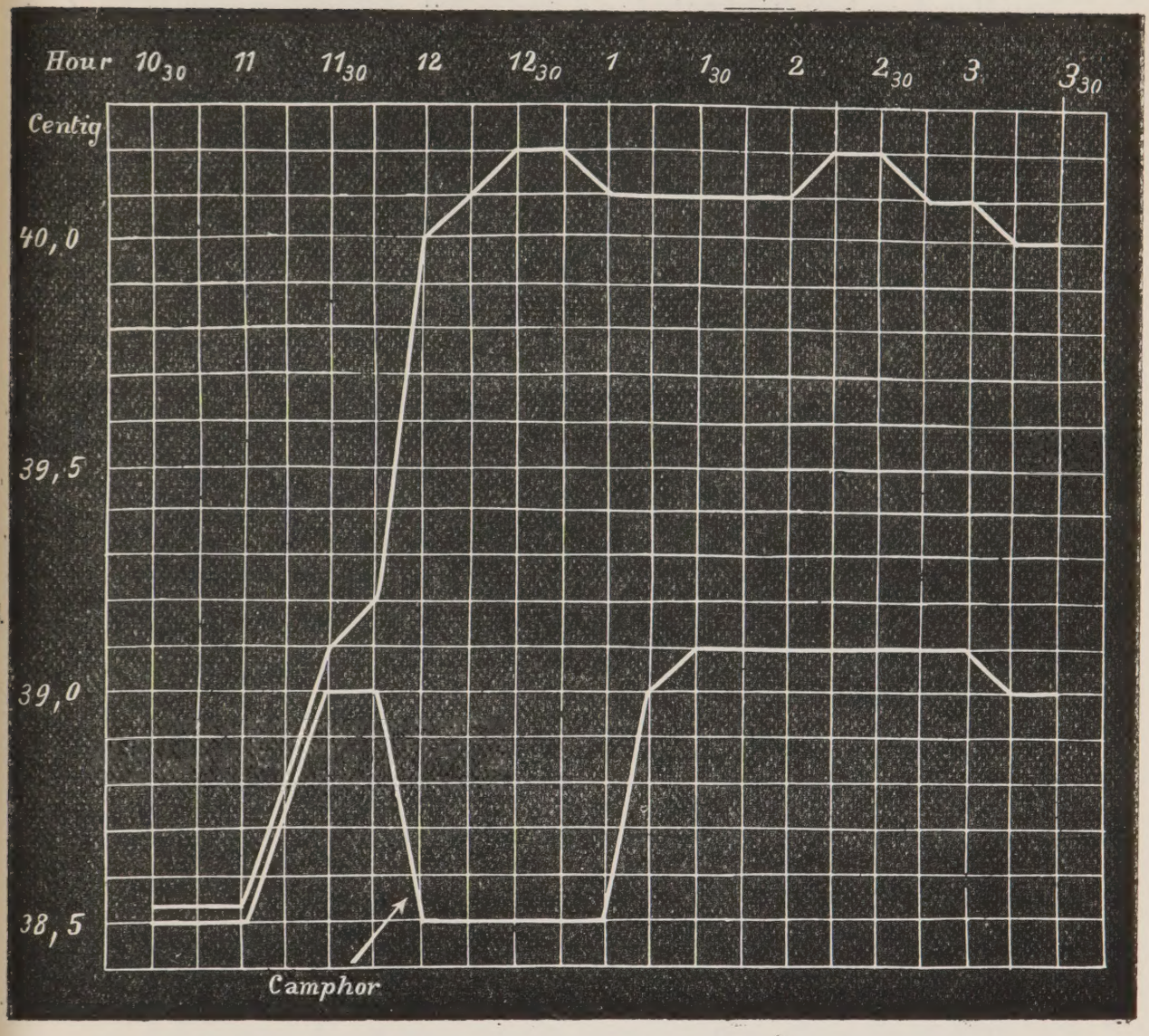
I do not know whether camphor will lower the temperature of septic fevers in human beings with the same certainty as it does in the case of animals. I must also leave it as an open question whether this drug lessens fever by its action upon the micro-organisms, upon the nervous system, or upon the circulation, or by a combination of these three factors. Its use in fevers is not of recent date, as may be seen from the following title of a work by L. H. Hencher, 'De igne per ignem extinguendo, seu de præstantissimo Camphoræ usu in febribus acutis,' Wittenberg, 1792.

Further, we can reduce the temperature of healthy animals by non-fatal doses of camphor, but not so easily. This effect, in both the healthy and the febrile state, was also produced in certain experiments[2] which were made under my

[1] J. Baum, 'Centralbl. f. d. med. Wissensch.,' 1870, s. 467; 'Beiträge zur Kenntniss der Kampferwirkung,' Bonn, 1872, Doctordiss. ; C. Binz, 'Arch. f. exper. Path. u. Pharm.,' 1875, Bd. v, s. 109.

[2] H. Kyll, "De effectu quem habet Camphora in Erysipelate," together with five thermometric experiments upon animals, 'Doctordis-

FIG. 30.



supervision as far back as 1865. These, with others of a later date, showed that the view which prevailed at that time among medical men, that camphor raised the temperature, was incorrect. This has since been corroborated by a further series of experiments at Dorpat.[1]

Camphor has also been found useful as a STIMULANT TO THE HEART AND NERVOUS SYSTEM in cases of threatened collapse. This is another instance of clinical experience anticipating experimental research. The subcutaneous injection of 0·1 to 0·4

sertation,' Bonn, 1866; these experiments were arranged by me, but were interrupted by my being called upon to serve in Bohemia as a surgeon in the army.

[1] W. Hoffmann, 'Doctordissert.,' September, 1866.

gramme (1½ to 6 grains) of camphor dissolved in oil, the smaller dose being repeated in a few hours, will cause a marked improvement in all kinds of disease when the pulse is failing, or has even become imperceptible. Although the results formerly obtained, when this remedy was given by the mouth, fell short of the above, they were essentially the same. It was invariably found, in the experiments of Baum, referred to above, that the heart of a warm-blooded animal to which moderate doses of camphor had been given, continued to beat more forcibly, and for a longer time after death than that of the control animal. Other experimenters have also investigated this action of camphor on frogs' hearts, and have obtained similar results. It thus appears that what we have long known with regard to the effects of the drug on human beings, is also true with regard to its effects on animals.

In rabbits the RESPIRATION was increased from one third to one fourth of its volume, by doses of camphor which were not large enough to cause convulsions. If the animal had been previously placed under the influence of chloral hydrate this increase still took place, but more slowly and to a less extent; on the other hand, if morphine had been given to the animal, the camphor produced a more stimulating effect on the respiration than when chloral had been previously given, at least so long as the comparative effect of the two poisons could be observed. The action of the camphor was not so transient as that of ammonium chloride.[1]

The SUDORIFIC action of camphor has been compared to that of pilocarpine.[2] Marmé, experimenting upon cats, developed perspiration in all four paws so long as they were uninjured. If the sciatic nerve was previously divided on one side, camphor did not cause any perspiration in the corresponding paw. This entirely confirms the well-known fact that camphor can act as a sudorific in disease, and it shows that it does so by acting on some part of the central nervous system. The action of camphor differs from that of pilocar-

[1] A. van der Helm, "Versuche über einige arzneiliche Erregungsmittel," 'Doctordiss.,' Bonn, 1887; C. Binz, 'Centralbl. f. klin. Med.,' 1888, s. 25.

[2] Marmé, 'Nachr. v. d. Königl. Ges. d. Wissensch.,' Gottingen, 1878, s. 106.

pine, in so far as the latter also increases the activity of the peripheral portion of the sweat mechanism.

In the human subject camphor, when taken internally, increases the secretion of the bronchial mucous membrane. This probably depends on the same factors as the increase of perspiration. The remedy is on this account frequently employed in cases, in which viscid mucus has accumulated, or may possibly accumulate, in the respiratory passages.

Formerly camphor was only given by the mouth, but this method has the disadvantage which is common to all the ethereal oils, of causing, if the dose be too large or too frequently repeated, irritation, hyperæmia, and even inflammation of the stomach. It is better to employ subcutaneous injections of a solution of camphor in oil of sweet almonds, as the drug is then soon absorbed by the lymphatics; the oil itself is not absorbed for several days, but causes no irritation.

Camphor can only be pulverised when it is moistened with one of its solvents (alcohol, ether, chloroform); it is then known by the name Camphora Trita. The officinal Oleum Camphoratum of the German Pharmacopœia, a solution of 1 part of camphor in 9 parts of olive oil, is used for hypodermic injections. The Vinum Camphoratum, or camphorated wine, an emulsion of 1 part of camphor with 1 part of alcohol, 3 parts of mucilage of acacia, and 45 parts of white wine, is only employed in dressings.

Spiritus Camphoratus of the German Pharmacopœia is a solution of 1 part of camphor in 7 parts of alcohol and 2 parts of water. Spiritus Saponato-camphoratus is camphorated soap liniment, or opodeldoc (see p. 313), diluted with alcohol. Spiritus Angelicæ Compositus is the distillate of an alcoholic infusion of the root of *Archangelica officinalis*, the root of *Valeriana officinalis*, and the berries of *Juniperus communis*, mixed with 2 per cent. of camphor.

Camphoric acid has the formula $C_{10}H_{16}O_4$, and is prepared by oxidising officinal camphor. The crystals are generally small, white, and inodorous; they have at first an acid and afterwards a bitter taste. Both the acid and its compounds with the alkalies dissolve readily in alcohol, ether, and eighty parts of water. On account of its antiseptic properties

the acid is administered internally, more especially in enteric fever, cystitis, and pyelo-cystitis. This led to the discovery of the property which camphoric acid has, of CHECKING PERSPIRATION, and the drug has consequently been frequently used, as an alternative to atropine or agaricine, to lessen the night sweats of phthisis.[1] The fact that it produces no collateral effects gives it an advantage over these remedies. The usual dose is 2 grammes (30 grains), but in exceptional cases several doses, amounting in the aggregate to 3—5 grammes (45—75 grains), have been prescribed with advantage. If we wish to obtain the full effect of the drug it must be administered on an empty stomach, and not more than two hours before the patient expects the onset of the perspiration. Camphoric acid is excreted in the urine within a few hours of its absorption. It is evident that the reputed action of the acid in inflammation of the bladder, must depend upon this fact.

Apparently camphoric acid checks the perspiration of phthisical patients only; it must therefore, unlike atropine, act upon the essential cause of the perspiration, namely, the decomposing products which are formed in the cavities of the lungs. Atropine, on the other hand, paralyses the sweat nerves.

Next to camphor, OIL OF TURPENTINE is, among this class of remedies, the one which has been most used, and whose action has been most thoroughly investigated. It is prepared from TURPENTINE, a viscid, yellowish sap, or "balsam," obtained by making incisions in the bark of certain species of pines. It consists of a solution of resin in ethereal oil, and contains traces of formic and succinic acids. The officinal turpentine of the German Pharmacopœia is obtained from *Pinus Pinaster* and *P. Laricio*. The

[1] Fürbringer, 'Berl. klin. Wochenschr.,' vol. x, 1888, s. 571; K. Bohland, 'Arch. f. klin. Med.,' 1891, Bd. xlvii, s. 289.

ethereal oil is also prepared by distilling portions of the plants (Pineæ, Nat. Ord. Coniferæ) with hot water.

The German Pharmacopœia distinguishes between CRUDE and RECTIFIED oil of turpentine. The latter, when chemically pure, has the formula $C_{10}H_{16}$. Formerly North America, Russia, and Sweden were the principal sources of the crude oil. This substance is colourless or a pale yellow; it may be rectified by shaking it with six times its weight of lime water, and then distilling the mixture until about three quarters of it have passed over into the receiver. The rectified oil should be colourless, and its alcoholic solution should not change the colour of blue litmus paper which has been previously moistened with water. Its boiling-point is 160° C. (320° F.), and its sp. gr. varies between 0·855 and 0·865.

If oil of turpentine is exposed to the action of light and air, it turns yellowish and viscid, and develops an acid reaction, whilst its peculiar odour is modified and its boiling-point raised. The flask you see here contains oil of turpentine which has been exposed to the light; you will notice that the cork is bleached in much the same manner—though to a less degree—as after exposure to the fumes of nitric acid. Evidently the oil, under the action of the light, has absorbed oxygen from the air. Further, fixed resinous acids, carbonic acid, and the lower acids of the fatty series, together with hydrogen peroxide (H_2O_2) are also formed in the oil; whilst ozone, O_3, is present in the superincumbent air. The presence of hydrogen peroxide may be demonstrated by a simple experiment. I take a test-tube containing a dilute solution of potassium iodide, add a few drops of some oxidised oil of turpentine, and then shake the liquid. There is no change of colour. If I now add a few small crystals of ferrous sulphate, the solution almost immediately becomes yellow, owing to the separation of free iodine. A solution of pure hydrogen peroxide in water would give exactly the same reaction, but in this case some ferrous sulphate—a substance readily oxidised—must also be added, to liberate the active oxygen from the hydrogen peroxide.

The presence of ozone in the superincumbent air is shown

by the bleached and decayed state of the cork. This may be still more clearly shown in another way. I suspend above the liquid a strip of thin filter-paper which has been previously soaked in a solution of potassium iodide aud mucilage of starch, and then dried. I remove the strip twenty minutes afterwards, and dip it in distilled water. It immediately turns blue. Consequently the conversion of oxygen into its two active forms—hydrogen peroxide and ozone—depends upon the slow oxidation of the oil of turpentine.

Purkinje[1] makes the following statement:—"For three days I took a drachm of oil of turpentine, sometimes with sugar, but sometimes without any vehicle, as the unpleasant sensations to which the drug gives rise in the mouth and throat, soon passed away. Beyond the fact that my temperature was somewhat raised I experienced no inconvenience—such as derangement of the digestion—save that I became extremely sleepy; it was with difficulty that I kept awake; if I was in a comfortable position and not seriously occupied I readily fell asleep at any hour of the day. My thoughts flowed easily, but notwithstanding my indolent and sleepy condition my movements were quite free from any of the effects which are produced by true narcotics. Though I spent many hours of the day in sleep—which undoubtedly was very much disturbed—yet I slept more profoundly at night than usual, and felt none the worse for it. So far the action of the turpentine was altogether beneficial. I afterwards employed it with a view to its soporific effect, successfully in several cases." Purkinje goes on to say that when a few drops of alcohol were added to the same dose of the drug symptoms of "inebriation" were developed, doubtless owing to the more rapid absorption of the turpentine.

The following case is worthy of notice.[2] A boy, fourteen months old, swallowed about 15 grms. (4 drachms) of oil of turpentine. A few hours later the doctor found him in a state of coma; the child was pale and cold, his pupils contracted; his pulse was quick and hardly perceptible, but still regular; his respirations were limited to three in the minute, and râles could be heard all over his chest. The

[1] Loc. cit., s. 439.

[2] Ph. Midall, 'Lancet,' 1869, vol. i, p. 360.

coma continued for twelve hours, when some improvement took place; but the boy again became comatose, and died three hours later.

In experiments upon dogs, doses of from 8 to 30 grammes caused inflammation of the stomach and intestines, hæmaturia, and death from paralysis of the nervous centres.[1]

If we rub oil of turpentine into the skin it gradually produces redness and inflammation, the extent of this varying with the quantity and the degree of oxidation of the oil employed. The oil is much more irritating when strongly "ozonised" than when pure.

The following are the chief properties of oil of turpentine which have any medicinal importance:

It is an ANTISEPTIC and an ANTIZYMOTIC on account of its poisonous action on the lower forms of protoplasm. The hydrocarbon $C_{10}H_{16}$ sufficiently accounts for this, but it is probably aided by the nascent oxygen contained in the oil. The oil is employed in various ways externally, sometimes alone, sometimes in combination with other substances. When administered internally, turpentine is absorbed from the stomach and acts on certain septic conditions of the mucous membrane of the respiratory and urinary passages. We know, from the smell of the breath and from chemical analysis of the urine, that it circulates unchanged in the blood for some time, and that a portion of it is excreted, unaltered, in the urine. Inhalations of the oil with steam are much employed for the alleviation of affections of the respiratory passages.

Turpentine is also useful in CHECKING SECRETIONS from mucous membranes. This has been proved by clinical experience and confirmed experimentally by Rossbach,[2] who applied the oil in two ways, namely, mixed with water and mixed with air, to the mucous membrane of the trachea. His results differed under the two conditions.

When, by means of a simple contrivance, a current of air saturated with oil of turpentine, was applied to some visible mucous membrane, the secretion diminished, and

[1] C. H. Hertwig, 'Arzneimittellehre,' 1872, s. 204; F. Seitz, 'Arch. der wissensch. Heilkunde,' 1853, Bd. i, s. 621.

[2] Rossbach, 'Festschrift d. med. Fac. zu Würzburg,' 1882, s. 42.

finally ceased altogether, so that the membrane became dry: the secretion started afresh as soon as the current of air was stopped. In control experiments with pure air the secretion was increased. It follows that the diminution of the secretion in the first case was due to the turpentine. On the other hand, a few drops of a 1 to 2 per cent. solution of turpentine in water immediately increased the secretion, but at the same time diminished the quantity of blood in the mucous membrane.

Undiluted oil of turpentine made the mucous membrane of the trachea very dry, but at the same time hyperæmic; the epithelium was thrown off, and distinct ecchymoses, together with a croupy exudation, were produced.

According to Rossbach, therefore, oil of turpentine would appear to have a distinctly beneficial effect upon the mucous membranes of the respiratory passages; its aqueous solution stimulates the secretion of these membranes, in spite of the fact that it contracts the blood-vessels, and so lessens the blood-supply. These experiments may explain the action of inhalations of turpentine, and show that the drug would probably have a beneficial effect upon chronic catarrhs accompanied with swelling of the mucous membrane, and would tend to diminish chronic secretion. It is asserted from practical experience that the same favourable results may be obtained by the internal use of turpentine, and that this is due to the fact that the oil is excreted to some extent in the respiratory passages, and so acts locally on the bronchial mucous membrane.

Experience has also shown that oil of turpentine is useful in simple catarrh of the bladder.[1] The internal administration of about 15 drops five times a day may restore the acidity of the urine, relieve the pain, and check purulent discharges from the mucous membrane of the bladder. The condition of the urine should be watched, as in some cases these doses are followed by hæmaturia, which, however, quickly passes off when the medicine is discontinued.

An endeavour has been made to obtain the beneficial effect of oil of turpentine on the mucous membranes of the respiratory passages by sending patients to reside in pine

[1] Edlefsen, 'Arch. f. klin. Med.,' 1876, Bd. xix, s. 82.

forests. Pliny,[1] in speaking of the Italian pine woods, says, that experience has shown that those forests which furnish resin and pitch are very suitable for consumptive patients and for convalescents; that, at all events, the air there is productive of more benefit to them than taking fresh mountain herbs during the summer, or than even a voyage to Egypt.

The same opinion is frequently expressed at the present day. When it became known that oil of turpentine generated ozone, the supposed favourable properties of the air of pine forests were attributed to the fact that ozone was developed by the oleo-resin exuded from the trees, and by the oil in the leaves. We have, however, no authoritative experiments to show that the quantity of ozone in fir, pine, or birch forests is greater than elsewhere.

Oxygenated or ozonised oil of turpentine—that is, oil which contains nascent oxygen—can be successfully employed in the treatment of acute poisoning by yellow phosphorus.

It has been known for a long time that phosphorus loses its phosphorescence when brought in contact with oil of turpentine. This is due to the fact that phosphorus having a great affinity for oxygen, combines with the nascent oxygen contained in the oil, and becomes altered in character. In this way an external coating of phosphoric acid, which is non-luminous, is formed round the phosphorus.[2]

It has been the custom in lucifer match factories to recommend the workmen to wear a vessel containing oil of turpentine on their chest, and also to sprinkle the oil on the floor, in order to neutralise the noxious properties of the vapour of phosphorus. The power of the oil to act as an antidote in phosphorus poisoning was first proved by a man[3] who swallowed the heads of a large number of matches in order to make quite sure of poisoning himself, and then, thinking to accelerate their action, took 15 grammes (about 4 drachms) of oil of turpentine. Contrary to all expecta-

[1] Plinius, 'Historia naturalis,' lib. xxiv, cap. xix.

[2] A. Walcker, "Die Wirkung ätherischer Oele auf die Lösung des Phosphors in fetten Oelen," 'Ann. d. Physik u. Chemie,' 1826, Bd. vi, s. 125.

[3] Andant, 'Bull. gén. de Thérap.,' 1868, vol. lxxv, p. 269.

tion, the results were very slight. Other cases of a similar kind occurred soon afterwards.[1]

Obviously the oxygen contained in the oil of turpentine reacts with the phosphorus in the stomach and intestines in exactly the same manner as it does outside the body. Phosphoric acid is not poisonous. The great drawback, however, to the use of oil of turpentine in phosphorus poisoning is—as happens in all other forms of poisoning where chemical antidotes can be used—that the physician usually has no opportunity of administering the remedy until the poison has perforated the intestinal canal, when obviously the turpentine cannot exert any beneficial action. Still it is advisable to give the patient the benefit of the doubt, and administer 5 to 10 grammes (1¼ to 2½ drachms) of the non-rectified oil.

Oil of turpentine is distinguished from camphor by the fact that it does not cause spasm, and so may be prescribed in much larger doses.[2]

Oil of turpentine is partly excreted unchanged in the urine, which thereby acquires a distinct odour of violets—a fact which was known to the Romans. This odour is due to products resulting from the oxidation of the oil.

In dogs, at any rate, a further portion of the turpentine —this also holds good with regard to camphor—appears in the urine as compounds of glycuronic acid.[3] One of these compounds contains nitrogen; an aqueous solution of the other decomposes on standing, and a derivative, the probable formula of which is $C_{10}H_{16}O$, separates out in oily drops. The fact that the urine reduces copper oxide and turns the plane of polarisation to the left may lead to the erroneous idea that the urine contains sugar.

Terpinum Hydratum, terpine hydrate, $C_{10}H_{16}.3H_2O$, consists of brilliant, colourless, and almost odourless crystals, with a feebly aromatic and somewhat bitter taste. These, on heat-

[1] Sorbets, 'Gaz. des hôp.,' 1869, s. 254.

[2] L. W. Liersch, "Zur Vergiftung durch Terpentindunst (Terpentinanstrich)," 'Vierteljahrschr. f. ger. Med.,' 1862, Bd. xxii, s. 232.

[3] Schmiedeberg, 'Arch. f. exper. Path. u. Pharmak.,' 1881, Bd. xiv, s. 308; E. Baumann, 'Arch. f. ges. Physiol.,' 1876, Bd. xiii, s. 307; H. J. Vetlesen, ibid., 1882, Bd. xxviii, s. 478.

ing, sublime as fine needles; they dissolve in 250 parts of cold water or 10 parts of alcohol.

Terpine hydrate is oil of turpentine with the addition of three molecules of water. It is formed when the oil is left in contact with water for a long time, but is usually prepared by treating oil of turpentine with alcohol and a little nitric acid. It is employed for the same purposes as the oil, but especially for chronic bronchitis; and possesses the advantage of being free from the smell of turpentine, which to many people is very disagreeable. Terpine hydrate, even when taken for some time, gives rise to no unpleasant symptoms beyond some disturbance of the digestive functions, which may always be obviated by taking the drug on an empty stomach. Its dose is 0·2 to 0·5 gramme (3 to 7½ grains) administered two or three times a day.

R. Lépine was the first to introduce terpine hydrate into practice.

The next group of drugs consists of certain plants, or the ethereal oils and aromatic principles derived from them, which were formerly somewhat largely employed internally in painful affections of the female sexual organs: some of these drugs are still in use.

Valeriana officinalis may be taken as the chief representative of this class. The fresh root yields from ½ to 1 per cent. of a neutral oil, the amount varying according to the season, and the condition of the plant: on the other hand, the oil obtained from the dried root has an acid reaction, which is due to valerianic acid.

I was led, by the frequent employment of this drug as a remedy for nervous excitement, to consider whether its sedative action might not be demonstrated upon animals. As it was impossible to develop in animals the special symptoms which occur in the human subject, and with which we are here concerned, I had recourse to two

poisons—brucine and ammonium carbonate—which act as stimulants upon the spasm centres. Two rabbits of the same litter, which had been fed alike, were given sufficiently large doses of these substances to cause convulsions, one animal having previously been given, as an antidote, a dose of the ethereal oil.[1] The success of the experiment was complete. Here are some of the details :

Two grey rabbits were experimented with—V., weighing 1740 grammes, and A., weighing 1950 grammes. To V. a subcutaneous injection was given of 1 gramme of oil of valerian, and an interval of two hours was allowed to pass, previous experiments having shown that the oil was but slowly absorbed from the skin. Both rabbits were then injected with ammonium carbonate, the amount in each case being proportionate to the animal's weight, so that V. received 0·89 gramme, and A. 0·90 gramme.

About ten minutes after this injection A. becomes sleepy ; the animal falls on its side, and in about fifteen minutes is seized with most violent clonic spasms.

V. is still lively, and entirely free from spasm.

30 min.—A.'s spasms still continue, but are less violent.

V. appears to be in a normal condition, and struggles violently when seized by the ears.

45 min.—The convulsions of A. continue, but are gradually diminishing in strength at each attack. The stupor becomes still more profound.

V. is quiet, though it makes an energetic resistance if seized. Its respirations are somewhat accelerated and irregular.

60 min.—Condition of both animals unchanged.

75 min.—A. lies apparently indifferent to its surroundings ; it still has violent general convulsions from time to time.

V. is perfectly vigorous, and runs round the room.

90 min.—A. is less sleepy, and at times attempts to rise ; the convulsions are slight, and only occur at long intervals.

V. remains free from spasm.

105 min.—A. gets up : the convulsions have ceased ;

[1] The experiments are recorded by my pupil V. Grisar in his Thesis for the Doctor's degree, 1873 ; see also C. Binz, 'Arch. f. exper. Pathol. u. Pharmak.,' 1875, Bd. v, s. 114, und 1877, Bd. viii, s. 61.

they recur, but only in the hind extremities when the animal is pushed. V. as before.

120 min.—A. is now quite free from spasm, and remains quiet in a corner. Both animals completely recovered.

The OIL OF VALERIAN is not the only ethereal oil which possesses this striking property; I found that the OILS OF FENNEL, CHAMOMILE, EUCALYPTUS, and TURPENTINE also possessed it. Others have repeated my experiments, and have added OIL OF PEPPERMINT, &c., to the list.

Here are the details of an experiment with oil of turpentine:

Two young rabbits—T. = 520 grammes, B. = 530 grammes.

9.45.—T., subcutaneous injection of 0·25 gramme Ol. Tereb. in an equal quantity of oil of sweet almonds.

10.5.—Both 1 mg. brucine.

10.30.—B. runs about restlessly; T. is quiet.

10.45.—T., a subcutaneous injection of 0·25 gramme Ol. Tereb. as before.

10.45.—Both 2·5 mg. brucine in the course of 55 minutes.

11.42.—T., 0·5 gramme Ol. Terebinthinæ.

11.43.—B., violent attack of convulsions.

11.46.—T. in the same condition as before.

11.55.—B., violent attack of convulsions, in which IT DIES.

12.—T. lies quietly on its belly. It CREEPS FORWARDS when pushed. This is followed by a few slight spasms in its hind legs.

12.10.—Turns its head from side to side, changes the position of its fore-legs, clearly with the intention of finding a more comfortable position. Its respirations are strong and somewhat over 100 a minute.

12.30.—Licks the ear of the dead animal, which has been lying in front of it, for a long time.

12.45.—When pushed, the animal creeps forwards a little on its fore-legs. A gentle touch on the nose, whisker, or eyelids gives the usual reflex action.

1.—Condition the same.

3.—Paresis of hind legs still continues; condition otherwise normal.

3·55.—Eats some clover which is put before it. There are no further spasms.

These favourable experiments are not purposely selected from many doubtful ones; all the experiments practically gave the same results.

We see thus that, in warm-blooded animals, non-poisonous doses of the ethereal oils can subdue, or greatly mitigate, violent excitation of the reflex centres, which would otherwise terminate fatally.

It is evident, from experiments of the same kind in frogs, that we must attribute this sedative effect upon the nerves, to a directly depressing action on the cells of the spinal cord, the brain, and the medulla oblongata. The ethereal oils produce the same effect when the spinal cord is severed from the medulla oblongata; they will still either lessen or prevent the convulsions which follow an injection of brucine. This shows that the action of the oils does not depend upon a stimulation of those centres in the brain which inhibit reflex action. It is easily proved also, by well-known methods, that the motor end-organs are not paralysed as may be the case, perhaps, when curare is used. This was clearly shown in the experiments upon rabbits, by the fact that the animals retained the power of motion.

From a consideration of all the facts I arrived at the following conclusion :—In large doses the ethereal oils mentioned above, and probably others also, have a DIRECT SEDATIVE action on a healthy, but more especially on a morbidly sensitive CENTRAL NERVOUS SYSTEM.

It does not necessarily follow that the same results can be attained in human beings as in rabbits. It is, however, possible that a sufficiently large dose of a mild oil might produce the same results. The contrary is equally possible. Still my experiments were the first to throw any light on the results of clinical experience. Oil of valerian, oil of chamomile, and many others are found useful in painful and spasmodic affections of the internal organs. They exert a depressing influence upon the cells of the spinal cord, as was manifest in the above experiments; and since these vola-

tile but fairly stable hydrocarbons pass through the tissues, they probably affect the neighbouring tissues when they are absorbed from the stomach and intestines.

Such effects have been often described as resulting from the action of oil of turpentine. I will therefore only refer you to a paper upon the subject,[1] and further to the results obtained by the administration of oil of turpentine in conjunction with ether in biliary colic.[2] In the latter case it has for a long time been supposed that the turpentine and ether dissolve the cholesterine. It is, however, difficult to believe this,[3] because the mixture must reach the gall-stones in a very diluted condition. On the other hand, both the above remedies, by diminishing the irritation caused by the gall-stones, and by lessening the contraction of the bile passages round the concretions, can alleviate the violent pain, and also promote the passage of the calculi.

Mosler did not, as text-books have stated, detect the oil in the bile, but only recognised a peculiar resinous smell which had no resemblance to the odour of violets given off by the urine.

A further contribution to our knowledge of the sedative properties of oil of turpentine, and probably also of other ethereal oils, was made by the discovery that the number of respirations was decreased in animals when air containing oil of turpentine was brought in contact with their respiratory passages ; in a dog, for instance, the respirations decreased, within a quarter of an hour, by as many as twenty-one in the minute. The oils have a similar action when given by the mouth ;[4] they and their preparations are still used in inflammatory conditions of the respiratory passages, and act by lessening the cough.

Camphor cannot be used in such experiments on warm-blooded animals, as it gives rise to convulsions ; in frogs, on

[1] L. Martinet, 'Sur l'emploi de l'Huile de Terebinthine dans la Sciatique et dans quelques autres Névralgies,' Paris, 1823.

[2] T. F. Durand, 'Sur l'efficacité d'un melange d'Ether sulphurique et de l'Huile de Terebinthine dans Coliques hépatiques produites par les pierres biliaire,' Strassburg, 1790.

[3] Mosler, 'Arch. f. pathol. Anat.,' 1858, Bd. xiii, s. 45.

[4] Rossbach und F. Fleischmann, 'Pharmakologische Untersuchungen,' 1879, Bd. iii, s. 52.

the other hand, it shows a marked antagonism to those poisons which cause general spasms.

The flowers of MATRICARIA CHAMOMILLA contain a dark blue, almost opaque, thick oil, which on exposure to air and light soon turns a dirty green and brown colour. This oil is the active agent of the hot infusion of chamomile flowers, which has long been a popular remedy in painful affections of the intestines and pelvic organs. The oil is also prescribed alone, in doses of 3 to 5 drops on a lump of sugar.

The following experiment shows the feebleness of its action as a poison, and its influence on the vascular system.

One c.c. of undiluted oil of chamomile was slowly injected into the jugular vein of a dog weighing 3180 grammes. Although the slight operation was painless, the animal became restless.

Time.		Blood-pressure.
12		110—125 mm.
12.2	oil injected.	
12.15		110—115 ,,
12.30		85— 90 ,,
1		82— 86 ,,
1.30		92— 96 ,,

At half past twelve the animal was completely stupefied; at half past one, when let loose, it became alert, and made a rapid and complete recovery. Soon after the injection was given, the respirations rose to 160 in the minute, and were vigorous. They remained so for a time, and then gradually decreased to 128. The pulse, when the blood-pressure was lowest, was 166 in the minute; it rose to 180, and finally reached 200. As it was always full and strong, the decrease of blood-pressure must have been due chiefly to the arterial dilatation brought about by the oil of chamomile.

The leaves of MENTHA PIPERITA, peppermint, furnish an officinal oil, from which, after standing in a cool place (about 24° F.), a stearoptene, MENTHOL, or peppermint camphor, $C_{10}H_{20}O$, is deposited. Pliny[1] was one of the

[1] Plinius, 'Hist. Natur.,' lib. 20, cap. 53, "Illinitur et temporibus in capitis dolore."

first to mention the effect of peppermint in alleviating pain. In our time it has again come into prominence.[1] The officinal oil is given in doses of 2 to 6 drops, or menthol is rubbed on the skin over the painful branch of the trigeminal nerve. The latter method was introduced from China and Japan, where it has been practised for ages. The application of menthol produces a sensation of cold. The cold, the contraction of the vessels, and the penetration of the volatile camphor through the skin to the endings of the affected nerve, may very often produce the favourable results which have been attributed to the remedy.

Oil of peppermint has the same depressant action on the nervous centres of animals as the oils used by Grisar and myself in our experiments. It can be taken in large doses, and, like the other oils, does not act on the heart, or at all events not at first. In the course of the last few years menthol has established itself in medical practice, more particularly as a sedative and as diminishing reflex action.[2] I lay particular stress on its beneficial action in the continued vomiting of pregnancy.[3] The dose is about 0·05 gramme ($\frac{3}{4}$ of a drop) hourly, dissolved in alcohol and very largely diluted with water. Its action, however, seems to be uncertain.[4]

Menthol is thus described:—Colourless, brittle, acicular crystals, with the odour and flavour of peppermint, melting at 43° C. (109·4° F.). It is readily soluble in ether, chloroform, and alcohol, but very sparingly in water, though it imparts its aroma to the latter.

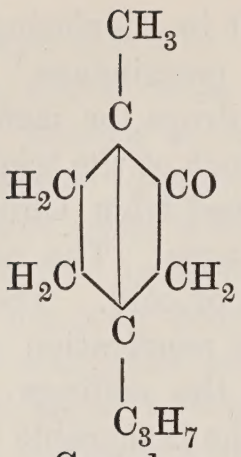
Even the empirical formula shows us the relationship of menthol to Japan camphor. The constitutional formulæ of the two may be thus represented (Bredt):

[1] Delioux, 'Gaz. méd. de Paris,' 1874, pp. 424, 447, et 484; A. D. Macdonald, 'Edinburgh Med. Journ.,' 1880, p. 121.

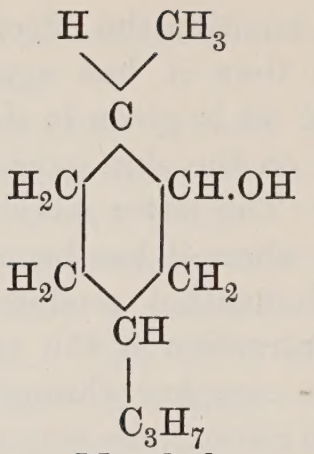
[2] For the literature on the subject see Langgaard, 'Therap. Monatshefte,' 1887, s. 100.

[3] S. Gottschalk, 'Berl. klin. Wochenschr.,' 1889, s. 875.

[4] Drews, 'Therap. Monatshefte,' 1890, s. 875.



Camphor
($C_{10}H_{16}O$).



Menthol
($C_{10}H_{20}O$).

The connecting link between the two is Borneo camphor, $C_{10}H_{18}O$, which is obtained from the wood of *Dryobalanops aromatica*, a tree growing in Borneo and Sumatra (see page 352).

Carum carvi, *Fœniculum officinale*, *Pimpinella anisum*, *Mentha*, *Melissa officinalis*, *Myristica fragrans*, the *Aurantiaceæ* of the Pharmacopœia, *Balsamodendron myrrha*, and other plants no longer officinal in Germany, were formerly described as CARMINATIVES. The name is still in use, and is best derived from *carminare*, which means to card wool. According to this view, it is supposed that when the stomach and intestines are sluggish and flatulent, they are stimulated by the ethereal oils of this group, and restored to a normal condition by the expulsion of the flatus. This may take place in three ways: first, by moderate stimulation of the secreting glands; secondly, by direct antizymotic action on those noxious ferments in the intestines, which give rise to the evolution of gas; and finally, by directly stimulating the peristaltic movement, and thereby expelling the accumulated gas.[1] All this corresponds with the effects produced by these drugs in the human subject. It is generally considered that only small doses of these oils are necessary, one drop or so repeated four or five times; larger doses give rise to hyperæmia and catarrh, and may paralyse the nervous centres. This effect has, for instance, been produced by taking a single nutmeg.

[1] The 'Schola Salernitana' devotes, cap. 49, the following hexameter fennel:—"Semen Fœniculi pellit spiracula culi."

The beneficial effect of small doses of the carminatives in promoting absorption and secretion in the stomach has also been demonstrated on dogs.[1] Oil of peppermint, of black mustard, and of ground white pepper were used for this purpose.

STERNANIS, *star-anise,* the fruit of *Illicium anisatum*, one of the Magnoliaceæ that grow in China, Japan, and the Philippine Islands, was formerly used as a carminative, and also—generally in the form of an infusion—as a means of lessening irritation in acute catarrh of the air-passages. This fruit contains sugar, a fatty oil, and a pleasant, aromatic ethereal oil, which is allied to oil of aniseed, as may at once be recognised by its odour. The star-anise is no longer officinal, mainly because of late years it has several times caused poisoning. It was mixed in these cases with the fruit of *Illicium religiosum*—named Sikkimi by the Japanese—which strikingly resembles *anisatum* in appearance, and even has the same odour of aniseed; it has, however, a bitter taste. As far back as 1834, J. Hoffmann pointed out its poisonous properties. His statements, however, were forgotten till a few years ago, when cases occurred in which star-anise caused convulsions,[2] irritated the bowels, and subsequently paralysed the nervous centres. A non-nitrogenous substance was discovered to be the active agent in these cases, 0·012 gramme being sufficient to kill a dog.[3] Chloral hydrate acts as an antidote when a minimum poisonous dose has been taken. Several persons were lately poisoned in Russia by "anisette," prepared from the star-anise.

The leaves of SALVIA OFFICINALIS, the garden sage, a plant belonging to the Nat. Ord. Labiatæ, indigenous in the Alps and cultivated in Germany, used to be much esteemed, as an astringent and antiseptic, in inflammation of the mouth and jaw. They contain about 1 per cent. of an ethereal oil with an agreeable odour, and also some tannin, but the latter

[1] J. Brandl, 'Zeitschr. f. Biologie,' 1893, Bd. xxix, s. 277.

[2] Langgaard, 'Arch. f. pathol. Anat.,' 1882, Bd. lxxxvi, s. 222; Falk, 'Vierteljahrschrift f. gerichtl. Med.,' 1883, Bd. xxxviii, s. 357.

[3] J. F. Eykmann, 'Husemann's und Hilger's Pflanzenstoffe,' 1882, s. 601.

is present in the fresh leaves only. The drug, after it has been kept, only contains gallic acid.

We must briefly consider the officinal aromatics—*Fructus Cardamomi, Rhizoma Zedoariæ, Rhizoma Galangæ, Rhizoma Zingiberis*, and *Fructus Vanillæ*, all derived from plants growing in hot countries. The last two, GINGER and VANILLA, are the best known. They have the same stimulating action on the stomach as the stomachics already mentioned, and in man they act also on the generative organs. The principal constituent of ginger is a complicated ethereal oil; that of vanilla is a camphor—vanilline—$C_8H_8O_3$, methyl-protocatechuic aldehyde $CH_3O.C_6H_3(OH).CHO$, which is found in the soft inner part of the fruit, and in the form of minute crystals, in its superficial layer. It can also be artificially produced by treating coniferine, $C_{16}H_{22}O_8 + 2H_2O$, with chromic acid. Coniferine is one of the glucosides which is present in the cambial juice of the Coniferæ.

Severe vomiting and diarrhœa have been repeatedly observed in individuals after taking ices containing vanilla.[1] We do not yet know how these poisonous effects are produced; they are certainly connected with the vanilla, and they may depend on some other ingredient being accidentally added in the gathering or packing, or on some fragment of the metallic box in which the vanilla was packed.

ARTEMISIA ABSINTHIUM may be placed in this group, as preparations of it have been much used as stomachics to promote digestion. Wormwood, however, is very important from another point of view. A liqueur is made from it which is very largely consumed in France. It had long been observed that results, other than those which are due to over-indulgence in alcohol, occurred in habitual drinkers of *absinthe*. In 1864 Marcé and Magnan undertook to try the effects of the liqueur on animals.[2] Various reports and numerous experiments were made with regard to it.[3] It is now

[1] A. Maurer, "Zur Casuistik und Aetiologie d. Vergift. d. Vanilleeis," 'Arch. f. klin. Med.,' 1872, Bd. ix, s. 303; Kupke, "Vergift einer Familie mit Vanille," 'Allgem. med. Centralztg.,' 1888, 14 April.

[2] Magnan, 'De l'Alcoolisme,' 1874.

[3] Challaud, 'Sur l'Absinthisme,' &c., Paris, 187; E. Lanceraux, "De l'Absinthisme," 'Bull. de l'Acad. de Méd.;' C. Bohm und Kobert,

known that oil of wormwood has the same effect as camphor upon the nervous centres.

This had already been observed some years ago by the medical attendant [1] of a man who had swallowed 15 grammes (about 4 drachms) of oil of wormwood. Convulsions of the face and limbs, loss of consciousness, and violent constriction of the throat were induced within a few minutes after the oil had been taken. Complete recovery took place, but, as is the case with most epileptic seizures, the man had no recollection as to how the attack began.

Magnan gave a dog of 14 kilos. weight, 5 grammes of oil of wormwood by the mouth ; in half an hour the animal had an "attaque d'épilepsie," ten minutes afterwards another supervened, and later on the dog distinctly suffered from hallucinations, and attacked a bare white wall, evidently taking it to be a ferocious enemy. A second experiment of the same nature is fully described by Magnan.

My own experiments with atropine, previously referred to, have repeatedly convinced me that genuine hallucinations of this kind do occur in dogs.

No further explanation is needed of the fact, that a substance which stimulates the brain so markedly should—when taken in excess day after day—set up by degrees such changes in the cells, the vessels, and the membranes of the brain, as would lead to that form of delirium tremens which is accompanied by characteristic epileptic seizures. The simple muscular tremor of delirium tremens is changed in the case of the absinthe drinker into an epileptic fit, which recurs from time to time. The fits cease if the habit is overcome during the early stages ; if the indulgence is continued there is permanent derangement of the intellect, ending in paralysis and death. The morbid changes vary according to the predisposition of the individual. The fits are sometimes more like hysterical attacks, in so far that peripheral anæsthesia may exist and consciousness be retained during the attack.

Folia Juglandis, walnut leaves, from the tree *Juglans*

' Centralbl. f. klin. Wiss.,' 1879, s. 689 ; Danillo, ' Arch. de Physiol.,' 1882, vol. x, pp. 388 et 599.

[1] Smith, ' Lancet,' 1862, vol. ii, p. 619.

regia. These, in their fresh state, yield an oil of a pleasant tea-like odour, which is not volatile at the ordinary temperature,[1] and hydrojuglon, $C_{10}H_5(OH)_3$, which is allied to naphthalene. Whether these two substances are contained in the dried leaves is uncertain. The leaves have a harsh and very slightly aromatic taste. The drug is only retained in the German Pharmacopœia because it is employed as a popular stomachic.

JUNIPERUS COMMUNIS furnishes the Fructus Juniperi—juniper berries—and the Oleum Juniperi, which are officinal. The ethereal oil is the active constituent of the berries, which are often employed to promote diuresis; the oil appears to act by stimulating the kidneys, and may even develop actual nephritis.[2]

Crushed juniper berries, together with equal parts of RADIX LEVISTICI—heartwort—one of the Umbelliferæ, containing an ethereal oil, with Radix Ononidis Spinosa—rest-harrow—and liquorice, form the officinal SPECIES DIURETICA, or diuretic tea. A well-filled table-spoonful infused in a large cup of water, is the dose.

CUBEBA OFFICINALIS, a climbing shrub belonging to the Nat. Ord. Piperaceæ, found in the East Indian Archipelago, has a small, round, wrinkled fruit resembling pepper, borne on a short, stalk; this fruit, gathered before it is ripe, is the officinal CUBEBS. Its utility in diseases of the urinary passages was known even to the ancient Arabian physicians. St. Hildegarde also mentions it in the following terms:[3]—"Cubebo calidum est, et calor ille temperamentum in se habet, et etiam siccum est. Et si quis cubebo comedit, indignus ardor ille qui in ipso est, temperatur." This dictum of the learned abbess of Bingen plainly refers to the treatment of contagious urethral catarrh. There are other passages in her writings which show that the noble lady was well acquainted with these particular disorders of mankind.[4]

Cubebs contains an ethereal oil, an amorphous acid resin,

[1] Report of Schimmel and Co., 1890, 'Chemikerztg.,' s. 1376.

[2] Simon, 'Versuche,' 1844.

[3] Edition of her works by Migne, Paris, 1853, s. 1141.

[4] For further details see C. Binz, 'Klinisches Jahrbuch,' Berlin, 1890, s. 7.

and a small quantity of a neutral substance which has been named cubebine. The action of these three substances has been demonstrated on the human subject.[1] Six grammes (or 1½ drachms) of the oil, taken within twenty-four hours, produced on the brain and on the alimentary canal the effects which are usually caused by ethereal oils. But the important point to notice here is that urination became somewhat painful, and that the oil reappeared in the urine only in a resinous form.

Ten grammes (2½ drachms) of cubebic acid, taken within five hours, acted similarly, though more gently, upon the brain and alimentary canal. The desire to micturate was more frequent, more uric acid was secreted, and the urine also contained undecomposed cubebic acid. The only effect of cubebine, $C_{10}H_{10}O_3$, even when as much as 16 grammes (4 drachms) were given in four doses during the twenty-four hours, was to increase the amount of uric acid.

I have known hæmaturia to be produced by the administration of too large a dose of powdered cubebs, but this passed off in a few days when the medicine was discontinued. The patient was a strong man, who had taken several teaspoonfuls of the powder at short intervals, in order to cure an attack of gonorrhœa as quickly as possible. It is for the treatment of this discharge that cubebs are chiefly employed. There is reason to suppose that the acid resin, whether already existing in the cubebs or formed in the body out of the oil, when it passes in the urine for several days over the affected mucous membrane, lowers the vital energy of the gonococci, in the same way as the direct injection of a solution of chloride of mercury, and other substances. The action does not take place through the blood, as was formerly believed; for Ricord observed, in the case of a person suffering from hypospadias, that, after the administration of cubebs and copaiva, the catarrh disappeared from that portion of the mucous membrane with which the urine came in contact, but that the portion over which the urine did not pass was unaffected.

[1] Bernatzik, "Die Cubeben physiologisch und chemisch untersucht.," 'Vierteljahrschr. f. prakt. Heilk.,' Prag, 1864, Bd. lxxxi, s. 9, und 1865, Bd. lxxxv, s. 81.

A cutaneous eruption of a papular or erythematous nature affecting the whole body has been often observed to follow the use of cubebs.

The resinous juice of the species *copaiferæ*, found in South America, constitutes Balsamum Copaivæ. It is a thick liquid of a light brownish-yellow colour, and has an aromatic odour and an acrid, bitter taste. A Portuguese monk towards the end of the sixteenth century observed that the natives of Brazil made use of it as a balsam for wounds. Its essential ingredients are an ethereal oil and an acid resin.

Mitscherlich noticed that oil of copaiva has the same kind of effect on healthy animals as oil of turpentine, but in a lesser degree. Bernatzik[1] found that it produced substantially the same results as oil of cubebs. A dose of 30 grammes (2½ drachms) brought on, within thirty-six hours, pains in the stomach, colic, diarrhœa, a sensation of burning in the urethra, and some difficulty in passing urine. There was an odour of copaiva about the urine, which contained about 7 per cent. of that substance in a resinous form. Fifteen grammes (about 4 drachms) of copaiva resin, taken within five hours, gave rise to violent vomiting, purging, severe colic, pain in the kidneys, and albuminuria. In another experiment, when 12 grammes (3 drachms) were taken, the albuminuria persisted for four days.

P. O. Rees observed that the urine of patients, to whom balsam of copaiva had been administered, was rendered turbid by the addition of nitric acid, although no albumen was present. Fr. Simon discovered in 1843 that this turbidity was due to minute drops of an oil which has the odour of copaiva and is readily dissolved in alcohol. H. Weikart proved that the above precipitate consists of copaivic acid.[2] Recent experiments have confirmed this.[3] The urine of a man who had taken one or more grammes

[1] Bernatzik, 'Vierteljahrschr. für prakt. Heilkunde,' Prag, 1868, Bd. c, s. 239; Kirchner, 'Berliner klin. Wochenschr.,' 1874, ss. 613 und 632.

[2] H. Weikart, 'Arch. d. Heilkunde,' 1860, Bd. i, ss. 176 und 567.

[3] H. Quincke, 'Arch. f. exper. Path. u. Pharmakol.,' 1883, Bd. xvii, s. 273.

of oil of copaiva during the day, acquired a rose and purple colour on the addition of hydrochloric acid; this reaction takes place more quickly if the urine is warmed: the precipitate is a resin. After the man had taken 1·5 grammes (22½ grains) of copaiva RESIN during the day the urine, on the addition of hydrochloric acid, gave only a slight precipitate, which was soluble in alcohol. On both occasions the urine reduced an alkaline solution of cupric oxide. When the balsam was administered the urine contained derivatives both of the oil and of the resin.

Copaiva retards the decomposition of urine. The well-known effects of the balsam on purulent, putrid, and infectious conditions of the urinary passages are no doubt to be explained in the same way as those which are produced by oil of turpentine and by cubebs. The constituents or derivatives of the balsam which pass into the urine have a paralysing action on those corpuscles which are about to migrate from the blood-vessels, check the alkaline changes caused by the secretion, and diminish the energy of the infectious organisms.

The efficacy of balsam of copaiva as a diuretic[1]—a fact which has long been known—seems to be due to its stimulating action on the renal epithelium.

BALSAMUM PERUVIANUM is the name of another balsam which may also be referred to here. A clear orange-brown liquid, very slightly if at all fluorescent, with a peculiar aromatic odour and a hot, bitter taste; it is insoluble in water, but soluble in alcohol and partially soluble in ether. It can only be obtained from certain limited districts of the State of San Salvador, in Central America. The bark of the tree *Myroxylon Pareiræ*, Nat. Ord. Leguminosæ, is loosened by bruising and cutting it with blunt instruments, and from this a small quantity of fragrant resin exudes. The flow is promoted by applying lighted torches or burning wood to the injured bark, which thus becomes charred, and in a few days falls off, when the balsam begins to exude from the stem. Rags are placed in the fissures to absorb the exudation; these are afterwards boiled in water and pressed. The balsam sinks to the bottom of the boiler,

[1] F. Brudi, 'Arch. f. klin. Med.,' 1877, Bd. xix, s. 511.

where it is left for several days, when the impurities float to the surface and are skimmed off, after which it is ready for the market. This preparation was named balsam of Peru because it was first shipped to Europe from the Peruvian port Callao, at that time under the dominion of the Spaniards, and the chief commercial centre in those regions.

The drug contains about 60 per cent. of cinnameïne, or benzyl cinnamate, $C_7H_7.C_9H_7O_2$, and benzyl benzoate, $C_7H_7.C_7H_5O_2$. It also contains about 10 per cent. free cinnamic acid, $C_9H_8O_2$, and a little free benzoic acid, $C_7H_6O_2$: the remainder consists of resin and a small amount of some aromatic compound, the nature of which is not yet definitely determined. It contains no ethereal oil, but recently an oil, said to be derived from this source, has been placed on the market.

Even before the Spanish conquest, balsam of Peru was used, both internally and externally, as a remedy in Central America. It soon found its way into Europe, and was employed internally in catarrh of the air-passages, the bladder, and other organs, and externally for indolent and foul ulcers and wounds. Wöhler and Frerichs experimented with it on a dog. Hippuric acid, a derivative of cinnamic acid, was found in the urine, which when heated with hydrochloric acid became blood-red. According to these authors part of the cinnamic acid is excreted unchanged in the urine—a point of some importance as regards the employment of this balsam in diseases of the urinary passages.[1]

Balsam of Peru, and cinnamic acid whether derived from the balsam or otherwise prepared, are both used at the present time in the surgical treatment of tuberculous disorders.[2]

Balsam of Peru is often adulterated with inferior balsams, resins, and viscid fatty oils, especially castor oil. The easiest way of determining any adulteration is by carefully testing the specimens according to the directions given in the German Pharmacopœia. If the balsam is pure, large doses

[1] Wöhler und Frerichs, 'Annal. d. Chem. u. Pharm.,' 1848, Bd. lxv, s. 339.

[2] A. Landerer, 'Münch. med. Wochenschr.,' 1888, Nos. 40 u. 41; 1889, No. 4.

can be administered internally without producing nephritis[1] or any other form of inflammation. R. Stockman in six hours took 14 grammes (3½ drachms).[2] His urine was not albuminous, but it contained a large amount of hippuric acid derived from the cinnamic acid. Loss of appetite and slight colic were the only symptoms. He gave 9 grammes to a large rabbit; on the following day its urine, when treated with nitric acid, gave a slight precipitate, similar to that resulting from albumen; but the precipitate disappeared on the addition of alcohol or of an excess of nitric acid, and was consequently not due to albumen, but probably to a resinous acid precipitated by the stronger mineral acid.

In the Charité at Berlin, balsam of Peru has been employed in the treatment of SCABIES,[3] as an agreeable substitute for the various irritating and unpleasant lotions and ointments generally used. The acarus is destroyed within forty minutes at the most, and the vitality of the eggs is also destroyed, though they resist for hours other pungent remedies, such as petroleum. A cure is effected in a few days, if the remedy is properly applied. The application of the undiluted balsam to the skin is not, however, altogether free from risk, as inflammation of the kidneys, with consequent œdema of the face and feet, has occurred after a single application of 20 grammes (5 drachms) to the whole body of a young person suffering from scabies, but otherwise in good health.[4]

STYRAX LIQUIDUS, prepared storax, is closely allied to balsam of Peru.[5] It is obtained by boiling and pressing the inner bark of the *Liquidambar orientalis*, a tree growing in Asia Minor, and belonging to the Nat. Ord. Hamamelideæ. It is a viscid, semi-fluid balsam, heavier than water, of a brownish-yellow colour, has a strong agree-

[1] Bräutigam und Nowack, 'Centralbl. f. klin. Med.,' 1890, s. 121.

[2] Ralph Stockman, 'Brit. Med. Journ.,' 1890, 14th June.

[3] Burchardt, "Die Krätze und deren Behandlung," 'Arch. f. Dermatologie und Syphilis,' 1879, Bd. i, s. 180.

[4] Litten, 'Charité-Annalen,' 1882, Bd. vii, s. 187.

[5] v. Pastau, 'Berl. klin. Wochenschr.,' 1865, s. 417; W. Schultze, ibid., 1866, s. 204.

able odour, and consists chiefly of cinnamic ether, styracine, or cinnyl cinnamate ($C_9H_7O_2.C_9H_9$). It also contains styrolene or phenylethene ($C_6H_5.C_2H_3$), free cinnamic acid, and free benzoic acid. Storax is the chief chemical source of cinnamic acid. Its destructive action upon the *Acarus scabiei* is much the same as that of balsam of Peru, whilst it has the advantage of being cheaper than the latter. It is generally mixed with double its weight of olive oil, and then rubbed into the skin. It sometimes, like balsam of Peru, has a transitory action upon the kidneys. Thus albuminuria was noticed nine times in one hundred and twenty-four patients suffering from scabies, after the use of an ointment consisting of 10 parts of storax, 10 parts of oil, with 1 part of alcohol.[1] R. Stockman swallowed 12 grammes (3 drachms) within three hours without experiencing any unpleasant effects. The same precipitate could be obtained from the urine of rabbits after giving them storax, as after giving them balsam of Peru.

Balsamum Tolutanum, balsam of Tolu, is the hardened resin of *Toluifera balsamum*, a tree indigenous to New Granada and belonging to the Nat. Ord. Papilionaceæ. It is a reddish-brown, crystalline mass, and may easily be ground into a yellowish powder which has a very pleasant perfume. It is soluble in alcohol, and the solution has an acid reaction. It is used as a coating for pills, as it is dissolved in the stomach or intestines.

The rhizomes of the *Iris germanica*, *I. pallida*, and *I. florentina* are also used for coating pills, to prevent them from sticking together. Each contains an ethereal oil which has a pleasant odour.

The following officinal drugs and their preparations are used for certain special and specific purposes:

Two kinds of the Persian *Ferula*, belonging to the Nat. Ord. Umbelliferæ, yield a milky fluid asafœtida, in which the active ingredient is an ethereal oil. This seems to be a mixture of $(C_3H_5)_2S$ and $(C_6H_{11})_2S$, and is related through the first of these bodies—allyl sulphide—to oil of Allium sativum, or garlic, which consists chiefly of that sulphide. Asafœtida has been prescribed in hysterical affections.

[1] P. Unna, 'Archiv f. pathol. Anat.,' 1878, Bd. lxxiv, s. 424

Jörg and his pupils experimented with it on themselves,[1] but experienced nothing beyond a slight amount of weariness and a feeling of great discomfort in the stomach and the intestines. Experiments with asafœtida on healthy women gave similar results. Asafœtida has recently been strongly recommended in Italy for cases of habitual abortion;[2] 6 grammes (1½ drachms) made into 60 pills are taken every two days as soon as the woman believes she is pregnant, and after a time this dose is spread over ten days. The drug may be employed internally in suitable cases, several doses of 0·1 to 0·5 gramme (1½ to 7½ grains) being taken every day. It is harmless, and we know that compounds like allyl sulphide have a sedative action upon the nervous system.

The genus *Cinnamomum*, grown in Southern China, yields Oleum Cinnamomi, which, as well as Tinctura Cinnamomi, is officinal. The greater part of the oil consists of cinnamomic aldehyde, C_9H_8O or $C_8H_7.COH$. On exposure to the air crystals of cinnamic acid are formed in the oil, owing to the absorption of one atom of oxygen by the aldehyde group COH. Oil of cinnamon is one of the ethereal oils with which Mitscherlich[3] experimented on animals. He states that it increases the frequency and especially the force of the heart's action; that when given in large doses it irritates the mucous membranes with which it comes in contact, and, as we are aware, paralyses the nerve centres. I refer to the oil here, as the tincture is still used to check hæmorrhage from the uterus, and to increase the activity of the uterine contractions in labour.

Several preparations of the ethereal oils are contained in the official Pharmacopœia, merely because they are employed in the preparation of various compounds which seem indispensable to many physicians. They are—

Aqua cinnamomi, Fœniculi, Menthæ piperitæ, all of which possess the taste and smell of the plants from which they are derived, and are formed by distilling the finely divided

[1] Jörg, 'Materialien,' u. s. w., 1825, ss. 345—384.

[2] G. Turazza, 'Centralbl. f. Gynäkologie,' 1892, s. 164.

[3] C. G. Mitscherlich, 'Lehrb. d. Arzneimittellehre,' 1849, Bd. ii, s. 144.

parts of the plants with water. In the preparation of Aqua Cinnamomi a tenth part of alcohol is added to the water.

Sirupus Aurantii Corticis, Cinnamomi, Menthæ—the finely divided parts of the plants are digested with water and alcohol; the liquid is then filtered, and sugar is added until it has the consistence of syrup.

Acetum Aromaticum contains 4500 parts of dilute acetic acid, 1200 parts of water, and 300 parts of alcohol, together with nine parts of a mixture of the oils of lavender, peppermint, rosemary, juniper, cinnamon, lemon-peel, and cloves. When aromatic vinegar evaporates ozone is formed.[1] The Acetum Aromaticum is used as a wash and for the purpose of inhalation. It is a clear, colourless liquid, has an aromatic and sour taste, and can be mixed with water in all proportions without becoming cloudy.

Mixtura oleosa-balsamica, Balsamum vitæ Hoffmanni, consists of ten parts of a mixture of balsam of Peru with the oils of lavender, cloves, cinnamon, thyme, lemon-peel, mace, and orange-flower, dissolved in 240 parts of alcohol. It is a clear yellowish-brown liquid, which is much employed as a liniment.

Species Aromaticæ—a mixture of peppermint leaves, wild and garden thyme, lavender, cloves, and cubebs—is used both for moist warm fomentations, and for filling bags (sacculi medicati), which are warmed and applied as dry fomentations for the purpose of checking commencing superficial inflammation.

Tinctura Aromatica is prepared by digesting cinnamon, cardamom, cloves, galangal,[2] and ginger in alcohol. It is prescribed in doses of from 20 to 30 drops.

The Pharmacopœia also contains the names of such drugs as Flores Sambuci and Flores Tiliæ, the hot infusions of which are still used as domestic remedies, and which in former times were the constituents of certain officinal compounds, such as Emplastrum Lithargyri Compositum and Tinctura Opii Crocata.

Several of these drugs and their preparations might be

[1] Wolffhügel, 'Zeitschr. f. Biol.,' 1875, Bd. xi, s. 427.

[2] *Alpinia officinarum.*

omitted without prejudicing therapeutics; the retention of them merely shows how strongly we cling to ancient customs.

Musk and castoreum may be included among the group of remedies containing the ethereal oils, as they are supposed to have somewhat similar curative effects. They are relics from those barbaric times when all human and animal excrements found a place in the medicine chest.[1] Castoreum has at last disappeared from the officinal Pharmacopœia of Germany, though musk is still retained.

Musk is obtained from the musk sac which is situated in the central line of the abdomen of the male *Moschus moschiferus*, the musk deer, between the navel and the penis, but rather nearer to the latter. This animal is only

[1] For details of this see C. Binz, "Zur Geschichte der Pharmakologie in Deutschland," 'Klin. Jahrbuch,' Berlin, 1890, s. 42, *et seq.*

Our predecessors, however, must not be held responsible for excremental pharmacology. It was a legacy from the ancient classical times which survived and was held sacred, like everything else which had been handed down to posterity, impressed with the venerated authority of Dioscorides and Galen. "Stercus humanum recens," says Dioscorides, "cataplasmatis vice impositum vulnera ab inflammatione vindicat simul vero glutinat; siccum autem cum melle perunctum anginosis auxiliari traditur. . . . . Humanam urinam suam cuique bibere prodest contra viperæ morsus et letalia pharmaca . . . pueri innocentis absorpta urina anhelantibus confert, cocta vero in vase cum melle." Galen, it is true, says that human excrement has an abominable smell, but at the same time he devotes a whole chapter to its discussion, and seriously states that a case of severe phlegmonous inflammation of the neck was cured by the employment of an ointment made from a mixture of the dried fæces of boys and Attic honey. In ten more chapters he sings the pharmacological praises of many other kinds of animal fæces; nor does he omit to advocate the use of the perspiration, saliva, cerumen, and urine of man. Who could have resisted such an example in the Middle Ages, when the books of Galen held the same position in regard to medical science as the writings of the most eminent fathers of the Church did in regard to theology?

found in Asia. The dried contents of the sac consist of a brown, granular, or somewhat soft mass of a peculiar, diffusible, penetrating, and persistent odour, which is perceptible even from the most minute quantity of the substance.

Aëtius, Court physician at Constantinople about the year 550, seems to have been the first to mention the medicinal use of this substance.[1] It has often been the subject of medical discussion since the sixteenth century,[2] but the experimental results which have been published concerning it are so devoid of definite facts that it is useless to refer to them.

Musk serves in practice as a stimulant or sedative according to the requirements of the patient. As a stimulant it is supposed to help the patient over dangerous crises in acute diseases, when paralysis of the heart is threatened;[3] as a sedative it is chiefly given in cases of spasm of the glottis in children. We must leave the critical examination of its value and use to clinical instructors. Some modern physicians think that it might be easily dispensed with. On the other hand, we must remember the opposition which arose from all sides in 1882, when the Commission appointed to revise the German Pharmacopœia proposed to discard it. Only four physicians in the whole empire declared themselves in favour of discarding it when the preliminary inquiries were made.

There is one thing which, at any rate, makes musk a medicine of very doubtful value, viz. its constant ADULTERATION. This is not easily detected, and yields a large profit, owing to the high price of the drug; the process commences even in Asia, directly after the musk is extracted from the

[1] Tetrabiblos iv, Sermo 4, cap. 122, 1567, p. 840.

[2] S. Albertus, 'Orationes tres: . . . . 2, de Moschi aromatis pretiosissimi natura et efficacia,' Nürnberg, 1585.

[3] Of the purely medical reports, two may be specially mentioned, J. Wall, 'Of the Extraordinary Effects of Musk in Convulsive Disorders;' A. Reid, "Of the Tunquinese Medicine," 'Philosophical Transactions,' 1774, vol. x, pp. 1044—1056. Reid gave 105 grains (6·3 grammes) within eighty hours in one case, among others, of a man suffering from a serious attack of rheumatic fever; the patient bore the musk very well, and recovered.

pouch, and it is carried on by the intermediate agents. The fact that nothing is known about its active ingredient is a second drawback to the therapeutic use of musk. The substances contained in the musk sac are those usually found in sebaceous follicles—fatty matter, albuminous bodies, soaps, cholesterine, traces of butyric acid and lactic acid, unknown extractives, and the well-known salts of blood-serum. The sac contains, in addition, like the follicles of the external sexual organs of most warm-blooded animals, certain odorous bodies, which in this case are more strongly developed than usual. The odour of dried musk is faint, but becomes more and more perceptible when it is moistened: the odour seems, therefore, to be continually generated in the musk. Acids and acid salts hinder its development. We have no further knowledge of its nature, and know even less about its pharmacodynamic importance. There has been a natural tendency to ascribe the action of this drug, as well as that of the ethereal oils, to the odoriferous substances, on no better ground, however, than one of analogy.

Musk is prescribed in doses of from 0·05 to 0·5 gramme ($\frac{3}{4}$ to $7\frac{1}{2}$ grains). Its TINCTURE is officinal. It has a strong odour of the drug, and is prepared by infusing one part of musk in twenty-five parts of water, and afterwards adding the same quantity of rectified spirit. It may be given in doses of 5 to 25 drops and upwards.

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